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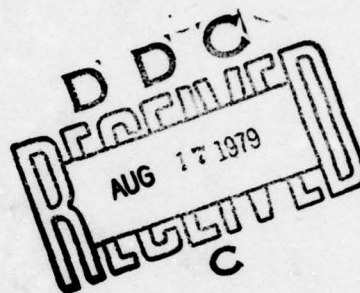
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VOLUME I
1978

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INTERNATIONAL CONFERENCE ON SCHISTOSOMIASIS

Cairo, Egypt • *October 18 - 25, 1975*



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PROCEEDINGS OF THE INTERNATIONAL CONFERENCE

ON

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Edited by Dr. H. H. H. H. H.

VOLUME I

Obtainable from the Director General, Institute of Research for Tropical Medicine

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SCIENTIFIC PROGRAMME

PLENARY SESSIONS

Saturday, 18 October 1975

11:00 **OPENING SESSION : INAUGURAL SPEECHES**

16:00—18:00 **EPIDEMIOLOGY AND SOCIO-ECONOMIC ASPECTS OF SCHISTOSOMIASIS**

Chairman : **Prof. D.H. Bradley**
Co-Chairman : **Dr. G. Webbe**
Rapporteur : **Dr. H.M. Hammam**

Sunday, 19 October 1975

09:00—11:00 **CHEMOTHERAPY OF HUMAN SCHISTOSOMIASIS**

Chairman : **Prof. A.O. Lucas**
Co-Chairman : **Prof. A. Prata**
Rapporteur : **Dr. M. Saif**

11:00—13:30 **MOLLUSCICIDE CONTROL OF VECTOR SNAILS AND CONTROL PROJECTS**

Chairman : **Dr. A. El-Halawani**
Co-Chairman : **Dr. M.A. Amin**
Rapporteur : **Dr. A. Lemma**

16:00—18:30 **IMMUNOLOGICAL ASPECTS OF SCHISTOSOMIASIS**

Chairman : **Prof. A. Capron**
Co-Chairman : **Dr. S.R. Smithers**
Rapporteur : **Dr. A.A.F. Mahmoud**

Monday, 20 October 1975

09:00—11:30 **ECOLOGICAL AND HABITAT CONTROL OF SCHISTOSOMIASIS**

Chairman : **Prof. D. Heyneman**
Co-Chairman : **Dr. Letitia Obeng**
Rapporteur : **Dr. W.R. Jobin**

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Tuesday 21 and Wednesday 22 October 1975

Convening simultaneously in Rooms A, B, C, D and E, with the same Chairmen and Rapporteurs, to discuss selected contributions by participants (Tuesday) and to prepare recommendations (Wednesday) and to discuss and adopt these.

PLENARY SESSION

Thursday, 23 October 1975

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Chairman : **Dr. N. Ansari**

Co-Chairman : **Prof. A. Woodruff**

Rapporteur : **Dr. A. Abdallah**

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P R E F A C E

Schistosomiasis in its different forms is estimated to affect at least 200 million people and endanger another 600 million in 72 subtropical or tropical countries or islands in Asia, Africa, the Caribbean and Latin America, creating public health problems of varying magnitudes. Schistosomiasis and malaria are the 2 most prevalent diseases in the world. Malaria, however, has received much more attention towards attempted eradication and control than has schistosomiasis. Yet with the introduction of water resources development projects including new irrigation schemes in the form of canals, drains, storage dams and reservoirs schistosomiasis is expected to increase. Although attempts at control have been made by international, national and private agencies, effective permanent results have not been achieved. Moreover, available technology is usually beyond the economic means of developing countries. There admittedly is still much to be learned about schistosomiasis and its effective control, yet it was generally felt that the time had come to put the basic knowledge already gathered to use and to apply this information to a world wide co-ordinated and forcefully directed international attack on this disease.

In June 1973 it was determined in discussions between the U.S. Office of Naval Research (ONR) and the Minister of Health, A.R.E., that an International Conference on Schistosomiasis was needed to start getting more basic knowledge put to use in an applied direction, so as to start controlling the disease. Towards this end the U.S. — Egypt Joint Working Group for Medical Cooperation, the World Health Organization and the United Nations Environment Programme jointly undertook the sponsorship of such a conference.

Financial support for the conference was obtained by agreements made between the Government of Egypt, the U.S. Office of Naval Research (ONR), the Center for Disease Control of the Public Health Service, U.S. Department of Health, Education and Welfare (CDC, PHS, DHEW) and the United Nations Environment Programme (UNEP). The Arab Republic of Egypt, as represented by the Ministry of Health (MOH, A.R.E.), was to plan and carry out the conference.

The envisaged aims of this conference were to convene scientific and economic experts, engineers, and duly authorized government and private administrators, so as to :

- determine the present state of basic research and applied research in all parts and aspects of schistosomiasis ;
- determine what was further needed in basic and applied research ;
- evaluate what direction basic and applied research should take to get schistosomiasis «under control» in the shortest period and at the lowest cost possible ;
- request the duly authorized administrators from the various international, national and private organizations invited to assume responsibility for conducting special portions of the research and studies determined by the body assembled to the best possible approach to a quick solution.

It was further anticipated that the various international or private organizations concerned would undertake this coordinated research and report on the progress to subsequent convened meetings of a body similar to the composition of the conference for further interchange on direction of research.

On October 18-25, 1975, the conference met on the premises of the National Socialist Union in Cairo. It was attended by more than 300 persons from 31 countries, including experts in various fields as well as duly authorized administrators of various national governments and representatives of private foundations and scientific institutions.

The conference was conducted on the following lines. Five main topics had been chosen by the Scientific Programme Committee, i.e. :

- Epidemiology, and socio-economic aspects of schistosomiasis
- Chemotherapy of human schistosomiasis
- Molluscicide control of vector snails, and control projects (of any type)

- Immunological aspects of schistosomiasis
- Ecological and habitat control of schistosomiasis (including biological control and related subjects).

Review papers by invited speakers and other suitable papers were read in 5 plenary sessions, each devoted to one topic, so as to afford general orientation to experts from different fields. In the subcommittee sessions, which proceeded separately and simultaneously, those papers were read and discussed which the Scientific Programme Committee had selected from the wealth of papers submitted to the conference, and which wholly or marginally fitted the chosen topics. Finally, after prolonged and exhaustive debates, recommendations were prepared by a workshop group for each topic and then presented to the conference as a whole.

Thanks are due to the National Socialist Union for providing their excellently equipped premises and conference halls for the Conference meetings and also to the Organizing Committee, the Secretariat, the interpreters and other staff, whose untiring efforts made possible the success of the Conference.

Ahmed Abdallah

Secretary General

NOTE TO PROCEEDINGS

The Proceedings of the International Conference on Schistosomiasis include the contributions read at the plenary and sub-committee sessions, either in extenso or in the form of abstracts. These papers are, on the whole, those specifically relevant to the 5 topics chosen by the Scientific Programme Committee (see Preface and Scientific Programme) although in a few cases they are only peripherally relevant to them or miscellaneous. They are all listed under the sessions to which they were assigned. Also included are some papers accepted, but not read, due to the inability of authors to attend the Conference.

Papers submitted to the Conference, but not accepted by the Scientific Programme Committee because they treated topics other than those chosen, are listed separately by title and author only.

The contents of the Proceedings are briefly summarized as follows :

VOLUME 1

Preface

Note to Proceedings

Inaugural speeches

Papers read, falling under the topics

- Epidemiology and socio-economic aspects of schistosomiasis
- Chemotherapy of human schistosomiasis
- Molluscicide control of vector snails and control projects

VOLUME 2

Papers read, falling under the topics

- Immunological aspects of schistosomiasis
- Ecological and habitat control of schistosomiasis

Titles of papers on other topics presented, but not read

Recommendations of Conference

List of participants

List of papers read, arranged alphabetically according to authors

Appendix : Action Plan on Ecological and Habitat Management of Schistosomiasis of the United Nations Environment Programme

The editor expresses his gratitude to Mrs. Anne Gismann for her help in preparing and editing these Proceedings.

Ahmed Abdallah

Editor

INAUGURAL SPEECHES

ADDRESS

by

H.E. Dr. Ahmed Fouad Mohy El-Din

Minister of Health, Egypt,

President of the Conference

Distinguished Guests, dear Colleagues, Ladies and Gentlemen,

It is a great honour to represent President Mohammed Anwar El-Sadat, President of the Arab Republic of Egypt, in inaugurating the International Conference on Schistosomiasis organized by the Egyptian Ministry of Health, the U.S./Egypt Joint Working Group for Medical Co-operation, the United Nations Environment Program, and the World Health Organization. It is a pleasure to welcome this distinguished group of scientists and investigators from various countries who have gathered to discuss the various aspects of schistosomiasis. I greet this indication of international co-operation in the study of an important health problem which exists in our country and in various other countries.

Schistosomiasis, as you all know, is a world wide problem, affecting more than 200 million people, in more than 70 countries. It is considered the second most prevalent disease in the world next to malaria. Since international efforts to-day co-operate in the combat against malaria in many areas, schistosomiasis is expected to become the world's foremost health problem. It is unfortunate that complete control of the disease is not in sight in the near future.

In our country schistosomiasis has been with us since the dawn of history. Recent studies indicate that, in all probability, the disease started around the great lakes of Africa and spread in every direction, becoming endemic in Egypt more than four thousand years ago. The Ebers Papyrus contained description of its symptoms, and calcified ova were found in tissues of some ancient Egyptian mummies. In 1851, Theodor Bilharz, the German

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scientist who worked in Cairo at the Kasr El-Ainy School of Medicine, discovered the adult worms in the blood vessels of human viscera and correlated this finding with the symptomatology of the disease. The British scientist Leiper, who worked in Egypt during the first World War, discovered the snail vectors of the disease in 1915 and elucidated the life history of the parasite. We have welcomed these discoveries by workers who have come to our country dedicating themselves to the benefit of humanity and accord them our profound respect, which demonstrates our policy and belief that science, working for peace, health and the prosperity of mankind knows no limits or frontiers.

Since the beginning of the present century, Egyptian scientists and workers have carried out pioneer work in the different fields of bilharziasis. A glance at the world literature on the subject testifies to their important contributions. Their work has aroused interest in the disease and its complications in tropical and sub-tropical countries as well as in South America and in the Far East.

Though bilharziasis is a world-wide problem, it is, for us, the prime health problem, related to our economic and agricultural progress, affecting millions at an early age, diminishing productivity and exerting a significant socio-economic impact. Agricultural expansion, as a result of irrigation schemes, is known to greatly increase the incidence of bilharziasis, a fact which makes the problem more severe and urgent.

We all realize that inspite of concentrated efforts, nationally and internationally over the past several years, no definite means are, as yet, available for the eradication of this important disease, or at least for its effective control. Improvement of the environment and raising the health and socio-economic standards, though highly expensive, does not suffice by itself. The use of molluscicides has contributed its share of benefits but has raised problems as regards their effect on human, animal and plant resources, especially in the long range. Treatment of patients on a large scale, though reducing morbidity, has not satisfactorily affected the incidence of the disease and has raised problems with respect to the side effects of the drugs used. Recently, attention has been focussed on immunity and the possibility of using its techniques for protection or for the prevention of occurrence of pathological changes. These studies, however, remain controversial.

The World Health Organization, had paid special attention in the past 20 years to the problem of bilharziasis. Several expert committees were convened and recommendations have been made, yet the 29th World Health Assembly which met in Geneva in

May 1975 considered that «The effort so far has not been proportional to the magnitude of the problem».

In 1974, the Egyptian Ministry of Health decided to organise this meeting and invite distinguished scientists and research workers in the field of bilharziasis in an effort to reach recommendations as regards the methods of control and to clarify problems related to several aspects of the disease, some of which I have already referred to.

I would like to mention that in this country we have spared no effort in the persistent combat against bilharziasis. From the time an Egyptian scientist, the late Mohammed Khalil Abdel-Khalek, introduced copper sulphate as a molluscicide in 1925, chemical agents have been extensively used. Chemotherapy has been administered to patients on a large-scale in different hospitals and health centers especially in rural areas. Efforts towards improvement of sanitation and health education have also continued over the years.

The Ministry of Health has implemented research in the field of bilharziasis. The Institute of Research for Tropical Medicine, founded over 40 years ago, has very significantly contributed in this research work. The Ministry has always welcomed co-operative efforts with international agencies and with other countries. A joint project with the World Health Organization has been operating in Beheira Governorate for 11 years to study the effect of systematic mollusciciding. Another joint project with the Federal Republic of Germany studied the effect of therapy plus snail control in the Fayoum. Currently two projects are being carried out, one with the World Bank in Middle Egypt and the other with The United States Government in Qaliub ; both aim at assessing the value of control through combinations of snail control, chemotherapy and covered drainage. The results of some of these projects will be presented in this meeting and, I am confident, will receive your attention for discussion and evaluation. The Bilharz Institute for Tropical Medicine provided with modern technological and scientific equipment is expected to start its activities next year.

Ladies and Gentlemen, allow me before closing to welcome again our distinguished guests : The U.S. Secretary for Health, the Director General of the World Health Organization, the Director of the Eastern Mediterranean Region of WHO, the Deputy Executive Director of the United Nations Environment Programme and all participants from the various countries. I wish them a happy stay in our country. I wish to thank the scientific and administrative committees for their efforts in the preparation of this conference and I wish this meeting every possible success.

ADDRESS

by

Dr. H. Mahler

Director General, World Health

Organization, Geneva, Switzerland

Mr. Minister, dear Colleagues, Ladies and Gentlemen,

It is a great pleasure for me to address this gathering of scientists and health administrators assembled here to discuss problems related to schistosomiasis in the country that could be justifiably considered as the homeland of the discovery of schistosomiasis and which has been responsible for much of the technical advances made in our knowledge of this parasitic disease and its socio-medical importance.

Many meetings have been held in the past few years at which progress in our knowledge of the parasite, its intermediate host, and the reaction of the definitive host to the parasitism was reported, in addition to the different biological, biochemical, immunological, immunopathological, clinical and epidemiological aspects, not to mention methods of control by chemicals, biological agents or chemotherapy. In fact, at this conference, emphasis will again be placed on reviewing such scientific observations and advances. Undoubtedly this is a necessary and, in fact, integral part of any approach to the control of parasitic as well as other communicable diseases.

But while not denying the significant progress made in technological development we must admit that we have been unable to launch any countrywide control or eradication programme with specific health technology in some twenty countries with more or less stable endemicity.

It is no secret that the maintenance of the transmission of endemic parasitic diseases is clearly related to human behaviour. It follows, logically, that unless human behaviour changes we would require a very powerful technology to cope with the disease and its consequences. The obvious question that arises is — have we considered all aspects in their holistic setting that favour the maintenance of the endemicity of schistosomiasis and have we objectively evaluated all the constraints mitigating against an organized fight against schistosomiasis? Have we, for example, explored all the methods social sciences have developed for promoting com-

munity participation ? Indeed how does one mobilize local and national will to control and eventually eradicate this disease ?

I am aware that in the coming days you will be attempting to answer such questions. Difficulties encountered in the application of available tools, i.e. chemotherapy and mollusciciding, their cost, side-effects, including toxicological effect on non-target organisms, are well known to you. But I am acutely aware of our deplorable scientific impotence in dealing holistically with MAN in this environment. The question is therefore — do we need or want a radically new technology ? Should we not rather combine the conventional technology with non-conventional, even non-medical technology ?

Today schistosomiasis is recognised as an important public health problem for seventy countries throughout the world where some 600 million people are exposed to the risk of infection and some 200 million are actually infected. I would say the point has been reached where realistically planned action is needed. The WHO is committed to collaborating with its Member States in undertaking activities aiming at reducing the level of endemicity, or even eradicating the disease where possible, with a combination of the conventional and non-conventional methodology available. But WHO must have the multidisciplinary support and advice of scientists all over the world who could contribute to imaginative solutions of the complex problems inherent in schistosomiasis control and eradication.

Schistosomiasis has so far remained mostly in the hands of the scientific community. This had had the advantage of increasing our knowledge. However, the time has now come for the politicians and the health administrators to take this problem into their hands with the aggressive support of the scientists. These decision-makers, in turn, should take over the problem not only as a medical problem, but as a socio-economic development problem. I do not need to mention how important the development of water-management schemes as a source of energy and increased agricultural production is for the Third World. However, such schemes can bring about an explosive spread of schistosomiasis unless decisive measures are taken to prevent this. Indeed schistosomiasis is an outstanding example of how health can claim partnership in social and economic development.

First and foremost health can claim such partnership as a contributor, and this in view of the increasingly obvious validity of the equation that development equals motivation plus knowledge. We know from social science studies that even people living at the

lowest subsistence level are ready to sacrifice a substantial proportion of their income in search of somebody or something to alleviate their suffering caused by their negative health status. Also, it seems to be a fairly undisputed axiom that communities with high levels of ill-health just do not mobilize their potential for developmental participation. Many well-intentioned economic planners have not yet been sufficiently sensitized to social poverty and to the related consequences of overlooking man's energy as the most critical input to socio-economic development.

Health, however, is also the great beneficiary of development. It is, of course, quite possible, and often essential, to launch isolated specialized campaigns against certain widespread diseases, but over the long-term such campaigns make only a marginal contribution to WHO's constitutional concept of health as a universal human right to a socially optimal level of individual physical and mental wellbeing. In that context health promotion depends first and foremost on such factors as nutritive food, safe water, a clean environment and a decent shelter, and thereafter on a readily available health care system which places the overwhelming emphasis on prevention. It follows then that health must be intimately interwoven in the total developmental process.

Yet another reason why health can claim partnership in development is the remarkably low cost benefit investment ratio stemming both from the almost insignificant per capita cost if health is treated as an integral part of overall socio-economic development and from the immediate impact of health improvement on the level of individual and community well-being and thereby on their motivation to participate aggressively in overall socio-economic development.

For these fundamental reasons health is claiming its proper place in development. When health has been rejected or treated with indifference by development planners, as has often been the case, the costs have been sky-high and often socially counter-productive.

We all proclaim our readiness to contribute to improving the quality of life. Control of schistosomiasis is one aspect which can bring about better conditions for millions of people in rural areas in Africa, Asia and Latin America. There is no need for big words and declarations. As Goethe said : In the beginning there was action. Are we ready for that action ? I hope the discussions at this conference will answer this question and I wish you every success in this task.

Thank you.

ADDRESS

by

Dr. Theodore Cooper

Assistant Secretary of Health, Department of Health, Education and Welfare, Washington, D.C., U.S.A.

Mr. Secretary-General of the Conference, Mr. Minister, the Director-General of the World Health Organization, the Deputy-Director of the United Nations Environment Program, other distinguished Conference participants and guests.

On behalf of the United States of America, and particularly as Co-Chairman for the United States of the U.S./Egypt Joint Working Group on Medical Co-operation, I am pleased to have an opportunity to take part in this vitally important international conference.

It is quite fitting that this conference is convened in Egypt where schistosomiasis, that ancient parasitic disease, was first recorded by Egypt's scientists. History tells us that the disease was identified in an ancient papyrus in the Nile Delta some 3500 years ago. Even in those distant times people were taught about the spread of this disease. They were advised to beware of infected water, which at that time, as it does today, contained the free-swimming cercariae of *Schistosoma haematobium*. Schistosomiasis has survived into the modern age. It is prevalent in Asia, Africa, Latin America and the Caribbean. It affects an estimated 200 million people and ranks with malaria as one of the two most prevalent diseases in the world.

Aware of this situation, the Secretary of State, Dr. Henry Kissinger, at the 29th Session of the U.N. General Assembly, called for an action campaign directed toward controlling the disease. This was followed by action at the 28th World Health Assembly which called upon the World Health Organization to initiate a concerted effort.

Even before the Secretary's statement at the U.N. General Assembly the Ministry of Health of Egypt was in the process of organizing this conference. We are grateful to the Ministry for its foresight and wisdom and for its efforts and hard work in the preparation of a meeting of this importance.

Also, I am pleased that the World Health Organization has risen to the challenge and that it has been joined by the United

Nations Environment Program, as co-sponsor of this very timely conference. We acknowledge their contributions with appreciation. The presence of participants from more than 28 different countries is testimony to the importance of the problem posed by Schistosomiasis.

I am sure that I speak for the entire U.S. representation here, the individuals of the U.S. Government and those from various institutions and private organizations, when I say that I am confident this will be a very successful conference.

The problem is a complex one which does not lend itself to a single or simple solution. This conference can, however, reinforce efforts to encourage health authorities and scientists all over the world to focus attention on Schistosomiasis as a significant health problem that can ultimately be resolved.

It is an opportunity for all of us to renew our efforts. It is a time for thoughtful exploration of ways to deal with this problem, which is not unique to this part of the world, but affects millions of people in the tropics and subtropics.

We are here because we recognise that a new look at Schistosomiasis is needed and that our efforts to forestall the continuing spread of this devastating disease must be strengthened. Amongst the things that we can do now are the following :

- Re-examine priority needs, identify major scientific, technical, economic, administrative and social problems that need to be solved.
- Determine where currently available strategies, known facts and techniques are applicable for the control of schistosomiasis.
- Identify and up-date various methodologies for determining the most rational allocation of resources, personnel and material, to control the disease in given areas.
- Research for additional avenues, new techniques and procedures for conquering the disease.
- And develop and provide specific recommendations for appropriate action in joint efforts to attack the problem on a local or regional basis.

We all recognise that one of the most important means of dealing with the problem of schistosomiasis is improvement in over-all social and economic status. It is important to remember that the accelerated search for new sources of hydroelectric energy and the intensification of food production through irrigation practices will extend the potential for transmission of schistosomiasis

and other water-associated diseases to new areas and populations. This consideration gives further impetus to the task before us.

Again I commend the organizers of this conference for providing this opportunity to examine schistosomiasis in all of its ramifications and to stimulate further public and international awareness of the many complex issues involved in planning and implementing activities for its control.

There is much work ahead for all of us who want to see this disease conquered. I am confident that through our joint efforts this conference will make a significant contribution toward a programme of control and will encourage the additional research necessary for prevention and treatment of the disease.

You have my best wishes for a very successful conference.

Thank you.

ADDRESS

by

Dr. Mostafa K. Tolba

Deputy Executive Director, United Nations Environment Programme (UNEP), Nairobi, Kenya

Your Excellency, Dr. Fouad Mohy El Din, Minister of Health, the Director-General of the World Health Organization, Dr. Mahler, Dr. Cooper, Dr. Taba, Dr. Ahmed Abdallah, Your Excellencies, Ladies and Gentlemen,

I regard it as a great honour and a special privilege to have the opportunity of addressing, on behalf of the United Nations Environment Programme, this important international conference. In spite of the fact that the conference is held in my own country, I yet am expressing the gratitude and appreciation of UNEP to the Government of Egypt, through you, Mr. Minister, for the keen interest and the efforts exerted to ensure the best preparations for the convening of the conference. We sincerely hope it will prove to be another milestone on the road of ceaseless efforts to control schistosomiasis.

Ladies and Gentlemen, the disadvantage of coming late on the list of speakers this morning is that it is difficult not to run the risk of being repetitive after the eloquent and fundamnetal statements made by Dr. Fouad Mohy El Din, Dr. Mahler and Dr. Cooper.

It is now increasingly recognized that the aim and purpose of development is changing, the concept of a better quality of life in both developed and developing countries is bringing to the surface new indicators for the measurement of the rate of development, and prominence is being given to alternative patterns and strategies for growth which the world community wishes to follow. The need for such alternative patterns emanates from a growing international awareness of the inter-relationship and inter-dependence of the various problems facing mankind ; of the complexity of cause and effect relationships which govern man's legitimate endeavours towards development ; and of the absolute necessity of finding ways and means of satisfying the inner-limits of the people on this earth, their basic human needs ; food, shelter, health, clothing, education and productive work without transgressing the outer-limits of the environment in terms of natural resources and the carrying capacity of the biosphere.

Thus, for UNEP, environmental considerations constitute essential elements of the decision-making process in development planning. They help provide the decision-maker with alternatives : whether to initiate actions with short-term benefits or to aim at a long-term sustainable development. It is within this general frame of mind that UNEP concentrates on what we label as environmentally sound techniques and bases its approach to the problem of environmentally sound management of pests.

The Governing Council of UNEP at three consecutive sessions urged that it should seek methods of approach, alternative to the use of chemicals, for control of pests. In that part of the environment programme, which deals with pests of man, animals and plants, schistosomiasis and malaria have been emphasized, along with cotton pests, as deserving of urgent concentrated attention.

In co-operation with the World Health Organization and the Food and Agriculture Organization, UNEP has prepared, for international meetings to consider, action plans for the ecological and habitat control of these pests. We joined the sponsors of the conference opening here today, to consider such action plans as they pertain to schistosomiasis. Last week, a meeting was held in Karachi, Pakistan, to consider ecological and habitat methods in the control of cotton pests and, in December of this year, there will be a meeting in Lima, Peru, on the bio-environmental control of malaria.

Both within and outside the United Nations system, extensive programmes for the control of schistosomiasis have been developed and followed, some of them for decades. The World Health Organization should be mentioned specially in this connection. The effort at control had been based largely on breaking the complicated life

cycle of the parasite, and in the application of methods, using chemical molluscicides, to destroy the snail intermediate host.

In the meantime a large body of evidence has been accumulating in the world indicating that most of the chemical treatments used have side effects which are likely to create hazards to both man and the delicately balanced ecosystems within which he lives. We are aware as well that in certain instances the principles of biological and ecological and habitat control of the host snails have proved to furnish potential methods of control.

The cultivation of suitable crop varieties as an effective means to reduce snail numbers has also been demonstrated by WHO, almost 10 years ago in Japan and the Philippines.

UNEP, with the help of a number of consultants who have extensive experience on schistosomiasis, has considered the elements requiring attention in a plan of action designed to use the modification of habitats and the function of natural mechanisms and ecological cycles and associations to control host snail populations and to break the life cycle of the schistosome parasite, with the minimum disturbance to the non-target organisms and the environment.

It is recognized that ecologically-oriented methods of control, however sound, cannot by themselves effect a break-through. We, in UNEP, believe, therefore, that a combined environmentally-sound attack on the snail host and the parasite's developing stages with effective immunology and safe chemotherapy for the human definitive host could achieve the break-through that we all seek for controlling the disease on a trans-national basis.

It would be naive to presume that the formulation of such a plan of action would provide a panacea. At the present stage of our knowledge, there are still gaps in our data base and in methodology, sometimes in crucial areas, which must be rectified if successful control is to be achieved.

The resources required for even a sustained research programme, let alone field experimentation and pilot projects, are likely to be on a massive scale. As such, they will exceed the financial capabilities of the United Nations Environment Programme and, I am sure, of the World Health Organization. They are likely to constitute a heavy burden on the government finances in any developing country. There should be thus a firm commitment on the side of the international community to support the implementation of control programmes.

We, therefore, hope this conference will be able to propose an articulated action programme covering application of existing knowledge, identification of research gaps, ways and means of

dealing with them and recommendations for training and exchange of information. It is of prime importance that the conference identify priorities, and time sequences. As far as the workshop of this conference dealing specifically with ecological and habitat management of the pest is concerned, the representatives of the various governments and institutions attending it are further requested to indicate where they feel competent to implement specific elements of the programme they will propose and wherever possible identify the sort of co-operation they are willing to assume among themselves to ensure the complementarity of their efforts towards the achievement of the goals of such a programme. If that is done, UNEP will be able to assume responsibility for certain aspects and exercise its moral influence to attempt to mobilize resources from other quarters for this most worthwhile cause.

Finally, Ladies and Gentlemen, it is left for me to wish participants to this meeting all success in their deliberations over the next several days. I am sure that your valuable inputs will help us all at the national as well as the international level to join forces to implement sound and practical strategies to combat the disease you are all concerned with as part of our concerned efforts to ensure a better quality of life for the generations to come on our «Only One Earth».

ADDRESS

by

Dr. A.H. Taba

*Director, WHO Eastern Mediterranean
Region, Alexandria, A.R. Egypt*

I am pleased and privileged to have the opportunity of addressing such a distinguished group of experts, coming from all parts of the world to discuss and exchange views on one of the most ancient diseases known in man, schistosomiasis, a disease of very great antiquity. To convene this meeting in Egypt, where the disease was first recorded four thousand years ago, is in itself interesting. The Ebers Papyrus of the sixteenth century B.C., contains what may be a reference to its treatment or prevention. Bilharz discovered the adult worm in Cairo in 1851, and, in our day, Egyptian investigators, with their broad experience derived from their own country, have enriched the literature on the subject with their publications on various aspects of schistosomiasis.

Schistosomiasis as a disease affecting the health, social well-being and economic potential of the population, has been, for a considerable time, the concern of national health administrations in almost all developing countries. At present, the problem is becoming of greater concern, not only to the national administrations, but to many international agencies involved in technical assistance and investment for health and socio-economic development.

The development of irrigation systems, entailing the increased spread of schistosomiasis, has aroused the interest of the public health workers and others concerned in the potential danger. Thousands of man-made lakes have been constructed or are under construction in many parts of the world, ranging from enormous waterbodies such as the High Dam in Egypt and the Euphrates Dam in Syria and other large dams in Africa, to modest-sized reservoirs elsewhere.

The building of dams and construction of man-made lakes have given rise to problems of human displacement and resettlement. Lake Nasser displaced about 120,000 persons in Upper Egypt and Sudan, Lake Volta displaced about 80,000 persons, and in the Euphrates Dam area, about 70,000 persons will be involved in the resettlement plan by the end of 1976.

While water development schemes are becoming the key to economic and social progress in many developing countries, the environmental changes due to these water schemes, with the concomitant social repercussions, can have far-reaching effects on the health of man.

Schistosomiasis at present ranks among the most important public health problems of the tropics and subtropics and is considered as second only to malaria, an estimated 180 million people being affected. The infection is widely distributed throughout Africa, the Eastern Mediterranean Region, Latin America and the Far East.

The Eastern Mediterranean Regional Office of the World Health Organization, has always attached great importance to the problem of schistosomiasis. During the last twenty years, many WHO-assisted projects for the control of schistosomiasis were implemented in many countries of the Region.

From the information collected from these WHO-assisted projects, as well as from research and control schemes conducted by Governments in the Region, many aspects of schistosomiasis have been disclosed, such as the epidemiological pattern of the disease, the biology and identification of vector snails and their ecology, the most suitable molluscicides, chemotherapy and methods of control.

However, we strongly feel that a global plan with a strategic approach is required for the countries to follow in their efforts to control schistosomiasis. To elaborate such a strategy will require further field study, basic research and training efforts. Accordingly, WHO has included schistosomiasis within its Coordinated Biomedical Research Programme and it will be a major subject of study in the WHO Special Programme for Research and Training in Tropical Diseases.

This Special Programme, broadly speaking, aims at the use of modern weapons of biomedical science to promote new means of action against the major parasitic diseases.

This International Conference on Schistosomiasis, which we are privileged to attend today, will be, I am confident, a distinguished medium for the leading investigators to exchange views, the outcome of which, will certainly support the impetus towards continued research, which will ultimately serve in building up a sound and effective control policy.

Ladies and Gentlemen, I wish you full success in your deliberations.

ADDRESS

AND PRESENTATION OF OFFICE OF NAVAL RESEARCH PLAQUES

by

Arthur J. Emery Jr.

*Scientific Administrator, Office of Naval
Research, Arlington, Virginia, U.S.A.*

I would like to take a few minutes at this opening session of the International Conference on Schistosomiasis to perform a few very pleasant duties.

As you know, an important international scientific meeting such as this cannot be held without the full co-operation of appropriate government officials. In the case of this particular meeting, we are very fortunate to have the full support of H.E. President M. ANWAR EL-SADAT and H.E. Dr. Ahmed Fouad Mohy El-Din, Minister of Health and his staff. For their support, I wish to express the sincere thanks of the United States Navy, and in par-

tical of the office of Naval Research. At this time I would like to read a letter addressed to H.E. A.F. Mohy El-Din, M.D.*

As all of you know, international meetings of this size take long periods of time to plan, organize and bring to a successful conclusion. Approximately 2 years ago, in a discussion between former Minister of Health, Dr. Mahfouz and me, it was decided that a meeting such as this was needed as guidance for our own respective agencies and countries and perhaps needed on a world-wide basis. Shortly thereafter when the Minister of Health officially approved this conference, Dr. Abdel-Moneim Aly, Director, International Health Department, Ministry of Health, A.R.E., was attending a post-doctoral course at the Johns Hopkins University School of Public Health and this was very convenient for me. It permitted us to meet as needed to make the initial plans for this meeting. At this time, I would like to read a letter addressed to Dr. Abdel Moneim Aly*.

Finally, when Dr. Aly and I started to plan this conference we agreed that there was only one person to serve as Secretary General for this conference. The Minister of Health approved our suggestion and Dr. A. Abdallah was imposed upon to accept this extremely difficult, time consuming and responsible position. During the planning period, Dr. Abdallah suffered a very unfortunate accident which necessitated his absence from Egypt for a period of time. However, Dr. Abdallah with the help of the Executive Committee and staff members of the Ministry of Health, kept the planning going in spite of all these problems. All of us certainly owe Dr. Abdallah a sincere expression of thanks for the excellent job that he, the Executive Committee and the staff of the Ministry of Health have done in bringing this important meeting to reality. In this regard, I would like to read a letter addressed, Dr. Ahmed Abdallah*.

Thank you for allowing me this time to draw specific attention to the efforts of those persons who have contributed greatly to this conference. Let us hope that it will lead to some solutions to the great problem of schistosomiasis.

* Letters from Rear Admiral R.K. Geiger, USN Office of Chief of Naval Research to Drs. Mohy El-Din, Abdel Moneim Aly and Ahmed Abdallah were read, and plaques were presented to each of them.

ADDRESS

by

Dr. Ahmed Abdallah

Secretary General of the Conference, Technical

Adviser to the Ministry of Health, Cairo, A.R. Egypt

Ladies and Gentlemen,

In the name of the Organizing Committee, and the Scientific Programme Committee, I sincerely welcome you and your participation in our conference. We all greatly appreciate and thank our colleagues who have travelled to Egypt from 31 widely dispersed countries in North and South America, in South-East Asia, in Africa, and in the Middle East, to employ their knowledge and their experience in the battle against schistosomiasis, to share in the discussions of the topics chosen and to fulfil the aims of our conference. I believe that this is the first time that such an August body has convened to discuss the different aspects of this disease on a global basis.

The Conference Scientific Programme Committee believes that all of the 5 selected conference topics are interrelated in the goal of controlling of schistosomiasis. The committee has therefore arranged that all participants whatever their specialized fields of experience will meet in plenary sessions in order that we all should be briefed, so to speak, on the problem as a whole as presented by our distinguished invited speakers in each topic. These presentations, as well as the papers to be read, will be discussed in the relevant specialized subcommittees which will meet separately and simultaneously during Tuesday and Wednesday.

It is expected, as outlined in the scientific programme we have distributed, that at the end of the discussions each subcommittee will form a workshop group to prepare a summary statement of the discussions and to suggest recommendations. A final plenary session will be convened to discuss and approve the recommendations made by the different groups during the conference.

The Scientific Programme Committee has also decided to provide most of the time available to the meetings of the subcommittees for discussions and consequently a selection has been made of the papers to be read in this conference. This selection was based upon the intimate relevancy of those papers to the subjects to be discussed. Copies of the abstracts of those papers are

at the disposal of participants at the secretariat. The other papers listed in the abstracts by title and name of author may also be discussed during the subcommittees' meetings whenever the occasion arises for such discussion.

Ladies and Gentlemen,

The aims of our conference are quite clear. On the one hand we will discuss our present knowledge and experience in the different topics and recommend the most effective and feasible method or methods of control available to us and the possible channels of implementation of control projects in different endemic areas. On the other hand we must identify the gaps present in our knowledge in the different aspects of the problem and recommend priorities for future research whose aim is, again, the finding of a better method or methods of control than those available to us at present. We all agree that this definition of priorities of research is a prerequisite to the establishment of a research programme and we believe that our discussions will guide us towards the identification of priorities that will hopefully result in the achievement of our goal of control.



FIRST PLENARY SESSION

Chairman's introductory note

**EPIDEMIOLOGY AND SOCIO-ECONOMIC ASPECTS OF
SCHISTOSOMIASIS**

David J. Bradley

Ross Institute of Tropical Hygiene

London School of Hygiene and Tropical Medicine

Keppel Street (Gower Street), London WC1E 7HT, England

Mr. Secretary-General, Officers and members of the conference, distinguished guests, ladies and gentlemen ; I find myself in a difficult position. To paraphrase an English saying : some are born chairmen, some achieve chairmanship and some have the chair thrust upon them. I am in the last category. Our distinguished and learned colleague, Dr. Willard Wright (formerly of the National Institutes of Health, Bethesda, Md.) is unfortunately unwell and has at the last moment had to cancel his attendance here. I suggest that we send him our warm greetings and wish him a speedy recovery. I will attempt to do justice to both our visions of the subject.

If there are any lessons that have been learned by all countries of the world in the last few years, if there are any lessons that have been forced upon us all, however unwillingly — and sometimes those of us who have been in the health professions, and most of all we physicians, have been unwilling to learn them — the most prominent of these lessons in the health field are two in number.

The first is that health is too important a matter to be left at the individual level. It affects the whole community too much to be left merely at the doctor-patient level. The poet's words :

"Send not then to know for whom the bell tolls, It tolls for thee."

are now accepted in the health field, several hundred years after they were written. We have to think not only of the sick person but also of the effects of his sickness on the community, and action to control his diseases must be at a community level as well. This is not new, it has been appreciated to some degree for many years but it has still not permeated the whole of our thinking. But it is being learned.

The second and more recent lesson that is being forced upon us is that health cannot be considered in isolation. Health is a part of overall development, of economic and social development. Conversely, a country cannot usefully think of economic and social development without considering health. Those of us concerned with health have, in part, to descend to the market place, or at the least to realise how what goes on in the market place affects us. Shifts in development emphasis affect health policies. If there was a single emphasis in economic development during the 1960's it was on growth and viewed in aggregate terms as growth of the gross national product. This was reflected in large central projects, whether for heavy industry or for hospitals, and

carried strong emphasis on urban areas with the hope of 'trickle down' to the rural populations. This emphasis has shifted, perhaps more in intention than in fact, so that if the preoccupation of the 1960's was with growth, that of the 1970's so far has been with distribution, that is, with how the benefits of development are spread among the population so that a larger number share in them. Inevitably this is related a shift from cities to the rural areas and towards the poorer people. This change in emphasis is as relevant to schistosomiasis as to any disease — rural development may tend to increase schistosomiasis, and those closest to the larger water development projects may not only fail to benefit from them but may have their health impaired following their implementation. It has been said that in no case have the inhabitants of an area flooded to produce a man-made lake ever benefited from it and usually they have been made worse off.

Conversely, it costs money to control schistosomiasis and those costs are in competition with many other development projects for the limited resources available.

There is no doubt, therefore, of the relevance of epidemiology and of economic aspects of schistosomiasis for our meeting. The social aspects have been emphasised already by Dr. Mahler. Their importance is as great as he has said, both in relation to causation and to consequences of schistosomiasis, but this lesson has perhaps not yet been adequately learned. When we look at transmission two crucial steps in the cycle are behaviourally determined: contact of people with infective water and access of excreta to that water. Yet only in the last few years have workers begun to study water contact behaviour seriously and less than

6 such studies exist. In the long term, attempts to get rid of schistosomiasis in a lasting way are likely to turn increasingly to basic hygienic improvements of water supplies and sanitation, yet facilities are of no benefit unless they are used. A simple approach to health education, in sites where human and financial resources are limited, has not proved outstandingly successful in promoting the use of environmental facilities. Greater understanding of how to change human behaviour is urgently needed.

Not only do social factors affect the epidemiology and control of schistosomiasis, but there is a converse effect. A disease that has limited economic effect in its milder forms may still make people feel very unwell and affect their lives, and there is no reason to think that schistosomiasis is an exception to this. Lassitude is widely considered a common feature of the disease. If, as Dr. Tolba has emphasised, we need to think increasingly of quality of life, social effects of schistosomiasis should not be neglected.

Because of these considerations it is right that this first plenary session should firmly place emphasis on the epidemiological and socio-economic aspects of schistosomiasis. This is the framework within which the technical approaches of subsequent sessions must justify themselves.

Our three speakers will look at the immense area covered by our topic of schistosomiasis in the community. Clearly they cannot attempt to cover it all, but are going to look at economic aspects, epidemiology in relation to control, and the effects of water developments on schistosomiasis, respectively. I shall attempt at the end to bring together their contributions and to fill any wide gaps between our speakers' areas of concern.

ECONOMIC JUSTIFICATION FOR SCHISTOSOMIASIS CONTROL

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Mr. Secretary General, Mr. Chairman, Members of the Conference, Ladies and Gentlemen.

Dr. Abdallah's invitation asking me to participate in this important meeting on schistosomiasis was received with mixed feelings. I was pleased to learn that the socio-economic effects of schistosomiasis were to receive consideration. Simultaneously, I was more than a little dismayed that it was I who was being asked to deal with this extraordinarily complex subject. Only after receiving considerable encouragement from several colleagues did I agree to attempt this important assignment.

My orientation is that of a physician — epidemiologist assigned to an international development agency.

Before proceeding with my remarks on the economic justification of schistosomiasis control, I wish to refer to the new resolution on schistosomiasis which was adopted by the last World Health Assembly of the World Health Organisation (WHA 28.53). This action was highly appropriate under current conditions of widespread malnutrition and increasing emphasis upon the expansion of agricultural production capacity through water management methods which favor the development of an increasingly serious

schistosomiasis problem. I feel confident that now it will be easier to obtain increased support for schistosomiasis. It does not necessarily follow, however, that health personnel in national governments or donor organizations will no longer be required to present convincing justifications to support proposed expenditures for schistosomiasis research or control.

For many years, authorities on schistosomiasis have considered it important to determine the economic effects of this disease. The need for such data is recognized also in WHA 28.53 which includes a request that the Director General of the WHO assist governments in planning and carrying out studies of its (schistosomiasis') social and economic impact.

Why should efforts be devoted to the development of an economic justification for schistosomiasis control? Howard (1972) in discussing the problem of developing a persuasive credible rationale for such control has said, «In absolute terms, resources are, of course, a limiting factor, in practice, resources tend to match the rationale. The problem is complex because of the number of players and the recognition that priority, like beauty, resides largely in the eye of the beholder». Howard's observation raises the question, who must be convinced? Within national governments of countries

where schistosomiasis is endemic the political leadership may respond favorably to requests for action by a concerned population. More frequently, it is national development planning commissions that require persuasion from Ministries of Health. The role of economists, which are usually well represented on such planning commissions, is to consider costs and benefits of proposed programs and to recommend approval of those which are most favorable toward the accomplishment of national policies. Increased agricultural production frequently is a national goal in less developed countries and it would appear to be in the interests of health ministries to devote considerable attention to the supply, health and motivation of the agricultural labor force. Because there is a strong association between agriculture and schistosomiasis in endemic areas, it follows quite logically that the effect of schistosomiasis upon the productivity and life expectancy of the labor force should be determined. This tends to become increasingly important because of the developing pattern of rural-urban migration and increased work that results for farmers through expansions in irrigation agriculture.

Like national planning commissions, international development agencies compare the merits of proposed projects. Such agencies in their endeavors to assist development in non-industrialized countries must necessarily make hard decisions concerning the allocation that will be made of finite resources. The process by which it is decided to support, to reject or to defer funding of projects is competitive. Health professionals serving in donor organizations often envy colleagues in other disciplines who can more readily justify their projects in economic and human terms. Agriculturists, for example, easily can justify projects that offer good prospects of increasing the

production of badly needed food or of commodities which assist national development because they earn foreign exchange. Similarly, engineers can point to the obvious direct benefits which will result from the construction of a new irrigation system or the economic development advantages that will be served by a new hydro-electric power scheme.

The main advantage which agriculturists and engineers enjoy over health professionals in the examples given above, is derived primarily from the products with which they are concerned. It is not as difficult for agriculturists to estimate annual increases in grain production that would be realized from an irrigation scheme, or for engineers to estimate the kilowatt hours of electricity that would be produced by a generating plant as it is for health personnel to estimate the number of economically significant cases of schistosomiasis that can be prevented annually by a control program. It is also easier for agriculturists and engineers to estimate financial values of their products than it is for health professionals to calculate the economic benefits of preventing new cases of schistosomiasis or preventing the progression of existing infections to disabling disease. Furthermore, malnutrition is a major health problem which cannot be solved without providing those in need with a satisfactory diet both in quantity and quality. This tends to increase the ability of any food producing programs to compete successfully for funds. Weisbrod *et al.* (1973) have described the dilemma of the decision maker, «The connection between economic development and the prevalence of a disease may be close enough to bring despair... there is a cruel equation at work in the world: irrigation or malnutrition; malnutrition or schistosomiasis». (Weisbrod, 1967).

Authorities on schistosomiasis, individually and as members of Expert Committees or Scientific Groups convened by WHO have often considered the deterrents to wider application of schistosomiasis control. The need both for appraisals of the economic consequences of schistosomiasis and of more data on epidemiological and clinical aspects of schistosomiasis which also bear upon economic impact of the disease is frequently mentioned.

The joint OIHP/WHO Study Group on Bilharziasis in Africa which met in Cairo in October 1949, was the first such group. It made the following recommendation :

«Quantitative knowledge is highly desirable concerning the relationship between the incidence and intensity of infection and the loss of productivity power of the individual and its economic consequences, and therefore, WHO should encourage studies to obtain such knowledge».

The WHO Expert Committee on schistosomiasis control in 1972 defined the important deterrents to a wider application of existing control measures (WHO, 1973). The report states, «Schistosomiasis Control Programs are still discouraged on the basis of the much repeated argument that the gaps in our knowledge of the epidemiology, public health and economic importance and pathology of the various forms of the disease are too large and that deficiencies in the medical infrastructure, shortage of skilled personnel, and the difficulty of ensuring a consistent flow of funds for projects of long duration form too great an obstacle. The Committee further noted that the lack of economic assessments was of particular importance when funds for disease control were sharply limited and those that are available have to be allocated rationally for control of the major endemic diseases in a country».

Ansari (1972) in an analysis of the situation with respect to schistosomiasis control made the following observation :

«Although there is much room for improvement, in fact the means we have at hand to control schistosomiasis are very good. If we agree that lack of adequate tools will not explain our problem with schistosomiasis control then the strategy of control must be reconsidered. But when strategy is reviewed we must face the problem of finance. We know from experience how hard it is to sell a program for control of a parasitic disease other than malaria. Those who decide on expenditure of public funds are usually not impressed by the urgency of controlling parasitic diseases. This condition might be changed if we had convincing evidence of their economic importance».

Schistosomiasis presents many features which, on superficial examination, appear adequately to justify long-term commitments of national governments and donor agencies to programs for its control. It is widespread, occurring in 71 countries and islands. Over 200 million people are infected among an estimated 600 million who are at risk. Except for Lesotho, every country on the African continent is known to be infected. In addition, schistosomiasis occurs in a number of countries in Asia and in the Americas. Its victims are predominantly impoverished rural populations. Improvement in the quality of life of the majority poor in non-industrial countries has been defined by the United States Congress as a primary objective of the United States' Foreign Assistance Program, an objective which the Agency for International Development shares with other development agencies.

Groups at high risk of acquiring schistosomal infections and schistosomal disease include fishermen and many types of agricultural workers. The health and labors of these groups now should be of paramount importance since increasing food production to meet the requirements

of rapidly increasing population is a major issue for the developing world. Meeting agricultural production requirements for human consumption and economic purposes requires that man-made environmental changes which enhance the transmission of schistosomiasis be continued and possibly intensified. Currently, it is estimated that worldwide 500 million acres of agricultural land are under irrigation as compared with 227 million acres in 1949 (FAO, 1973). Over the next 20 years FAO has recommended that this be increased by 48% or approximately 250 million acres (FAO, 1975). Not all of this development will occur necessarily in areas at risk of schistosomiasis, but several projects of which I am aware in fact are being planned in endemic areas. The potential for a worsening schistosomiasis situation may be further compounded if fertility rates remain unchanged and current demographic projections of population increases prove to be accurate. Globally, the 1975 population of 3.90 billion would increase over 80% to 7.2 billion by the year 2000. During this same period even greater percentage increases are projected for North and sub-Saharan Africa. The combination of intensified irrigation agriculture, large increases in suitable habitats for intermediate host snails, greater crowding of human populations and greater pollution of snail infested surface water by schistosome infected people provide ingredients that may well permit schistosomiasis to produce more damage than it has exhibited heretofore.

These attributes of schistosomiasis have, no doubt, contributed to the present recognition of schistosomes as disease agents which may well deserve far more attention than they have received previously. Whether or not this will be sufficient justification to initiate and sustain

the necessary programs to control schistosomiasis remains to be seen. The prudent course now appears to be one which will strengthen the case for schistosomiasis control to the maximum extent including, as soon as possible, a further assessment of the economic losses attributable to schistosomiasis on a community basis in at least one carefully selected worst case area.

Some difficulties that exist in developing an ideal justification may be seen by comparing schistosomiasis with diseases which have been, or now are, the subjects of special campaigns. Global or continental campaigns have been conducted against malaria, smallpox, urban yellow fever and yaws. At the outset, in the case of malaria, smallpox and yaws, methods existed which offered the possibility of eradication of the disease. In the case of urban yellow fever the feasibility of eradication was demonstrated during a program to control *Aedes aegypti* in Brazil. The cost of these programs was acceptable and it was expected that within a reasonable time all expenditures could be discontinued without a resurgence of the subject disease. By contrast, it is not expected that schistosomiasis can be eradicated using currently available methods except possibly in a few isolated foci. Hence, sustained long term funding is needed if control is to be maintained. Epidemics of urban yellow fever and smallpox with high case fatality rates over short periods of time can command public attention with or without economic justification. Yaws also calls much more attention to its victims because they are so much more frequently visibly afflicted. The slowly progressive nature of clinical schistosomiasis in many areas of the world has well protected these parasites against serious human efforts to eliminate

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them from the earth although control measures are employed regularly in some places.

Onchocerciasis on the Volta River Basin has presented two features which have made it possible to justify a control effort in a project area which encompasses about 650,000 km² in seven African nations. First, blindness has been accepted as having an obviously negative effect on the capacity of farmers to plant, tend and harvest their crops. Second, available evidence supports the contention that fear of onchocerciasis is directly responsible for the abandonment of an estimated 65,000 km² of fertile river valley. Although precise measurements have not been made to determine the effect of blindness on farmer productivity, and although some blindness may not be the result of onchocerciasis, the economic principles involved are quite clear. Avoidance of future blindness as a result of a successful control campaign should lead to increased productivity by future sighted farmers.

An additional economic benefit would be the agricultural production obtained from 65,000 km² of reoccupied fertile river valley. These two features have helped facilitate a favorable decision to support this project and now a multi-donor, multi-million dollar control program planned to continue for 20 years is in progress under leadership of the International Bank for Reconstruction and Development with the WHO serving as the action agency.

The task of producing an economic justification for control of schistosomiasis would be greatly simplified if it, like onchocerciasis, produced permanent blindness, or denied farmers the use of vast tracts of land in a nation with pressing food shortages. But schistosomiasis is much more subtle and consequently the task of justifying its control in cost-benefit terms is more difficult.

Part of the complexity of the problem arises when one attempts to obtain data on the cost of control. It soon becomes clear that there is wide variation from one project to another. The WHO Expert Committee on Schistosomiasis Control in 1972 (WHO, 1973), stated :

«Existing control programs have been estimated to have annual recurrent costs with a range of U.S. \$0.40-\$12.00 per capita».

If the annual cost per person at risk is U.S. \$0.40 and, worldwide, 600 million are at risk, the minimum cost for a global program in 1972, possibly earlier, would have been U.S. \$240 million. The comparable figure for an at risk population of 30 million would still be U.S. \$12 million annually. Some economists are beginning to show a preference for projects which have prospects of yielding an internal rate of return of 15% or more. If this were applied to our hypothetical population of 30 million who would be protected from schistosomiasis at an annual cost of U.S. \$12 million, economic productivity of the working members of the population would have to increase U.S. \$13.8 million/year. Assuming that of the 30 million population only 6 million were working throughout the year the necessary productivity increase to yield a 15% rate of return is U.S. \$2.30. An increase in the annual *per caput* cost of control to U.S. \$12.000 would produce a comparable productivity increase requirement of U.S. \$69.00 for the hypothetical population of 30 million.

Undoubtedly, the problem of project costs become much easier to cope with when one is dealing with a specific project although the reports of such costs are presented quite differently by different authors. Uniformity in reporting project costs would be helpful to those who endeavor to perform desk top research.

Economists with whom I have conferred concerning the possible benefits of schistosomiasis controls suggest that these be considered under the following 3 categories :

A. **Direct Benefits :** Expenses avoided, discounted into the future. Two examples of direct benefits are :

1. Savings which can be attributed to the control program because inpatient and outpatient services for schistosomiasis diagnosis and treatment are no longer needed.
2. Any welfare or disability payments which are avoided.*

B. **Indirect Benefits :** Examples of these benefits include :

1. Increased worker productivity and/or the economic value of deaths prevented.
2. Productive value of new land brought under cultivation.
3. Spillover benefits — (An example of such benefits would be profits to persons trading with the primary beneficiaries).*

C. **Others :** Perhaps intangible.

Examples include removal of a social stigma or more enjoyment in recreational activities.

Over and above the general problem of adequate records or reports on essential points, the key problem in determining the economic benefit is concerned with the evaluation of schistosomal infection and disease upon economic productivity.

Perhaps it would be wise to check first whether there exists any reasonable prospect for demonstrating that any or all of the major schistosome species can

possibly have a detrimental effect upon the economic productivity of workers, especially agricultural workers. Certainly, *Schistosoma japonicum* and *S. mansoni* are capable of producing total disability and premature death. Similarly, *S. hematobium*, because of its apparent close association with cancer of the bladder and its demonstrated lethal capacity to cause severe obstructive uropathy, has the potential for producing significant economic effects.

Considering that schistosomiasis has a potential to produce detectable economic effects why have not convincing economic data been presented already ? One reason appears to be that severity of pathology and intensity of infection varies widely from area to area and few efforts have been made to determine severity of disease in entire communities. Sites have not been selected for the purposes of assessing the economic impact of schistosomiasis upon community productivity but rather have been determined by the location of individuals who had an interest in the subject. All too frequently this has led to biased studies of workers, excluding anyone who was disabled by advanced schistosomal disease. Another reason is that health personnel have failed to include in their studies the high level of detailed data which economists require and the one study conducted by economists was not in an area that can be considered a severe problem area.

Of the four studies which have attempted to measure output of agricultural workers, one was in an *S. hematobium* endemic area of Cameroon and the workers there were cane cutters (Gateff *et al.*, 1971). Two investigations were conducted at different periods on the same sugar cane estate in an *S. mansoni* infect-

* Some economists do not feel these items can be considered benefits.

ed area in Tanzania (Foster, 1967; Fenwick, 1972 and Fenwick & Figenschou, 1972). The remaining study also in an *S. mansoni* infected area, examined workers on a banana estate, private banana growers, and a comparison group working in a paper plant, all in St. Lucia (Weisbrod *et al.*, 1973).

The Cameroon study failed to demonstrate any significant adverse effects of *S. hematobium* infection, and, in fact, indicated that infected workers were more productive, though not statistically significantly so, than were those who were uninfected. This can hardly be taken as conclusive evidence that *S. hematobium* has no economic significance anywhere. Hence, consideration of further investigations into the economic significance of *S. hematobium* infections and disease are indicated. However, because it is important that individuals be grouped not only according to different levels of intensity of infection but also according to clinical gradients of disease, studies of *S. hematobium* patients will be more difficult to perform on a community basis than will studies of *S. mansoni* or of *S. japonicum*. This is true because palpation of enlarged livers and spleens is much simpler to perform on large populations than are X-ray visualizations of the urinary tract.

The three *S. mansoni* studies offer encouragement for proceeding with further investigations in *S. mansoni* areas that can be classified as worst case situations. Preferably, any such investigation would be undertaken in an area free of other causes of hepatomegaly or splenomegaly especially malaria and Kala Azar.

The study of Foster (1967) in Tanzania indicates that infected workers imposed significantly greater costs on the sugar cane estate for medical care than

did those who were uninfected. While at work however, output of infected workers did not differ significantly from their uninfected counterparts but the absentee rate was significantly higher among infected workers.

Fenwick (1972) and Fenwick & Figenschou (1972) retrospectively compared bonus earnings of cane cutters infected with *S. mansoni* against those of uninfected controls. Mean bonus earnings of uninfected workers were consistently higher in all of the consecutive six-monthly time intervals but only in one period was the difference statistically significant. In a follow-up study the change in bonus earnings of infected workers was determined after the administration of anti-schistosomal therapy. During a one year period, post-therapy earnings increased a dramatic 28.1%. Earnings of this group before treatment had been 12.5% less than that of the uninfected controls but following treatment, control worker earnings exceeded that of the treated workers by only 6.5%. Fenwick, after examining the cost of the estate schistosomiasis control program, reductions in direct costs for medical care, and increased productivity, concluded that this control program was cost effective. Regrettably, this is the only study to date which has arrived at that favorable conclusion.

The study of Weisbrod *et al.* (1973) in St. Lucia, from the economists' point of view, has undoubtedly been the most rigorously designed economic assessment of schistosomiasis that has been conducted to date. Regrettably, they were unable to demonstrate that schistosomiasis and several other parasitic infections in the area, either singly or in various combinations, were economically significant with respect to learning ability in school, fertility, or productivity on the job. The

lone exception was the significant result obtained from *Strongyloides* which reduced days worked, weekly and daily earnings of female, but not male, agricultural workers.

Though these results may be disappointing they hardly can be viewed as the final answer on the economic consequences of schistosomiasis. Jordan's (1972) admirable review of the great differences that exist in the severity of schistosomiasis from one area to another and the strong cause and effect relationship that appears to exist between intensity of infection and clinical gradients of disease must be considered in the planning of future assessments of the economic impact of schistosomiasis. As Weisbrod *et al.* (1973), point out, a demonstrable reduction in labor productivity may well be absent because schistosomiasis is of recent origin in St. Lucia. Though the first case was discovered in 1924, significant spread of the disease did not begin until the 1950's. It may then be that the maximum potential of schistosomiasis had not been approached when this study was undertaken. Now that control measures are being applied, that potential may never mature fully. Weisbrod and his co-authors have conducted a very thorough and credible critique of this work which I shall not dwell upon. Admittedly, the effort in St. Lucia was to determine the effect of schistosomiasis upon the productivity of

workers and more data indeed are needed on this matter ; but should not those of working age who have been totally disabled be included in the lost productivity equations ?

In conclusion, I wish to express my own belief that although more concerted efforts may now be made to control schistosomiasis, competition for funds will continue within the health sector and between the health sector and other sectors which more visibly contribute to economic development.

The future of schistosomiasis control will be brighter if investments in control can be demonstrated to enhance economic development and to provide necessary protection to the health of agricultural workers.

Because expansion of man-made water management projects favors an increasing severity of the detrimental effects of schistosomiasis, and because no economic studies of this problem have yet been conducted in an area known to have a high prevalence of disease, a new economic study is needed in such an area to determine the worst that schistosomiasis can be on a community basis given time and favorable conditions. Such a study whether cross sectional or longitudinal should be developed jointly by economists and by biological authorities on schistosomiasis.

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EPIDEMIOLOGY OF SCHISTOSOMIASIS AND PROSPECTS FOR CONTROL

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The epidemiology and control of schistosomiasis have been adequately reviewed by different workers and several expert groups in recent years (Jordan, 1972; Miller, 1972; WHO, 1973; 1975; Hoffman, 1975). I therefore propose to briefly discuss only certain significant aspects of these fields as a basis for highlighting certain gaps in our knowledge and providing an appreciation of the prospects of significant progress in control of the problem.

Diagnosis

While considerable advances have been made in our knowledge of many facets of the epidemiology of schistosomiasis during the past 15 years, probably one of the most important advances has been the development of new methods of measuring egg excretion which have enabled workers to make more accurate determinations of the relationships between prevalence and intensity of infections in a variety of epidemiological situations. Qualitative methods of egg detection are important in individual and epidemiological diagnosis, but improvements are desirable in their sensitivity. The available quantitative techniques also require greater sensitivity for more accurate detection of low density egg outputs and improved quality of descriptive epidemiology; better evaluation of control measures involving estimates of preva-

lence, incidence and intensity of infection; and more sensitive pathological and chemotherapy studies. Automated methods of egg-counting should be explored in order to increase the efficiency of epidemiological surveys involving large numbers of people.

The immunodiagnostic techniques which are now available for routine use are wanting in accuracy, sensitivity and specificity and can only be used in epidemiological investigations or for individual diagnosis in a supplementary role to the parasitological techniques. A recent meeting of investigators on the immunology of schistosomiasis (WHO, 1975) considered that an immunodiagnostic technique for schistosomiasis should be both specific and sensitive, quantitative and applicable to mass surveys, and that its value would be enhanced if it assisted in identifying active infection, and if it could give information on the immune status of the host. It was concluded that two developments are required for the improvement of immunodiagnostic tests: the preparation of pure antigens and the development of tests using only very small amounts of these antigens. Recent progress has been made in these fields and affinity chromatography, using either specific enzyme inhibitors or immunosorbents, now makes it possible to produce acceptable quantities of highly purified antigens by moderately simple procedures. Three

schistosome antigens have been prepared using this method: acetyl cholinesterase, a genus-specific antigen, and a species-specific antigen. Three highly sensitive techniques are now available for detecting antibodies to very small amounts of these antigens — radio immuno assay, the defined antigen substrate sphere (DASS) method; and the enzyme-linked immunosorbent assay (E.L.I.S.A.). It is likely that these new techniques will prove useful in field studies, but it must be emphasised that all the available techniques are diagnostic only, there being no evidence of correlation between any serological parameter and protective immunity.

Recent observations (Madwar & Voller, 1975; Phillips & Draper, 1975; Smith et al., 1975) suggest that either free antigen or antigen antibody complexes can be detected in a considerable proportion of patients with schistosomiasis although previous experimental observations indicated that antigens can be detected only in massively infected animals. The circulating antigen was detected by a gel diffusion method and complexes were revealed either by splitting with citric acid and detecting both antibody and antigen by counter current immuno-electrophoresis or by the demonstration of inhibition of complement dependent rosette formation. These observations appear to be of 'immediate relevance for the diagnosis and understanding of some of the pathological features of schistosomiasis' (Nelson, 1975).

Intensity of infection

Cheever (1968) found that *Schistosoma mansoni* worm burdens were higher in patients with Symmer's fibrosis than in asymptomatic subjects and that there was a near-linear relationship between worm burden and the number of eggs per

gramme of faeces. This latter observation suggests that quantitative studies of egg output should provide an estimate of the relative intensity of infection in different age-groups and therefore an index of the worm burden in a community. Smith et al. (1974) however, studying egg excretion and tissue egg burdens in urinary schistosomiasis in Egypt, suggested that egg excretion as an index of tissue egg burdens or intensity of infection should not be interpreted without consideration of the stage or activity of the disease. Emphasis is now being placed on investigations of intensity of infection and Jordan (1972), commenting on data from Brazil, Tanzania and St. Lucia, has drawn attention to the relationship between prevalence and intensity of infection and the fact that small differences in prevalence, particularly where this is high, may be associated with considerable differences in intensity of infection and therefore possibly of prevalence of clinical disease. It is clear that more clinical surveys are necessary together with egg output studies, in order to correlate intensity of infection with resulting disease in clinical and pathological terms.

Consideration has recently been given by a study group (Hoffman, 1975) to the relative merits of longitudinal epidemiological studies and cross-sectional studies in determining the relationship between intensity of infection and subsequent disease; evaluating the economic and social consequences of schistosomiasis in areas where it is thought to be a significant cause of morbidity and mortality; obtaining quantitative confirmation of the importance of the disease in different geographic areas and in different epidemiological and social environments; and studying the relative importance of schistosomiasis in relation to other health problems of an endemic area. A longitu-

dinal study may be the only approach to investigate a particular question where adequate time and resources are available. But there are other serious disadvantages, including the changes which may occur to influence the results over a long-term period and ethical considerations. In some instances it may be difficult to justify the cost of a longitudinal study and demonstrate that it provides results which could not be obtained by a cross-sectional assessment.

Larval stages of parasite

The free-living stages of the parasite have not been extensively studied in most past epidemiological investigations. The use of the 'sentinel' snail exposure technique (Upatham, 1970), does however offer a method of obtaining quantitative information about the contamination of a particular habitat with miracidia and an estimate of the inoculation rate of snails. The inoculation rates of naturally infected snails have been calculated from their infection rates (Sturrock & Webbe, 1971) and the results were found to be similar to those obtained from exposures of sentinel snails. Further epidemiological studies are required of the relationship between contamination and the degree of infectivity of different transmission foci.

Similarly, further efforts are needed to estimate numbers of cercariae in natural habitats. The use of sentinel rodents has proved of value but provides only indirect information on cercarial densities and is expensive for routine epidemiological studies. The efficiency of direct filtration techniques has been improved (Sandt, 1973a,b) and clearly quantitative data on cercarial concentrations are of the utmost epidemiological significance.

Immunity

Particular research problems which require epidemiological study include ob-

taining precise information on the longevity of adult worms and egg output, and determining the relationship between different patterns of cercarial exposure and the resulting intensity of human infections. Such studies are of course related to an understanding of the mechanism of acquired resistance to schistosomiasis which may play a significant role in the epidemiology of infections. Although it is generally considered that immunity to reinfection develops in man, conclusive evidence has not been obtained. Nevertheless circumstantial evidence from epidemiological studies can be used to support the concept (Pesigan *et al.*, 1958; Clarke, 1966; Kloetzel & Rodriguez Da Silva, 1967; Bradley & McCullough, 1973; Ongom & Bradley, 1972; Omer & Amin, 1973). In the majority of endemic areas age-specific prevalence rates increase to a peak, usually in the second decade of life, and then decline. This is commonly found in the case of the three main human infections. The extent of the decline in prevalence in the older age-groups varies in different endemic areas and for all three species, being greatest in *S. haematobium*, which probably reflects different immunological responses. The intensity of infection as measured by egg output in stools or urine also varies with age and shows a similar pattern to prevalence. The fall in prevalence and intensity of infection in adults may therefore be attributable to resistance to reinfection and the gradual spontaneous death of worms acquired during infancy. In Rhodesia, Puerto Rico and St. Lucia, however, quantitative water contact studies all show that adults have less contact with water than children and observed reductions in prevalence and intensity of infection might be due to such reduced water contact together with spontaneous death of worms.

At a recent meeting of investigators (WHO, 1975) it was concluded that available evidence suggests that immunity is probably not a controlling factor when prevalence and intensity of infection are light, but that in areas where infection is moderate to severe, some immunity appears to develop in the older age-groups. In areas of high transmission it was considered possible that tolerance to the parasite may develop, thus preventing the development of resistance to reinfection.

It is, therefore, clear that further additional well-designed epidemiological studies of prevalence, incidence and intensity of infection in endemic areas are needed. Studies should also be made of reinfection patterns after chemotherapy among people living in endemic areas, and of the longevity of worms in populations which have moved to non-endemic areas, or following effective control programmes. The design and evaluation of control programmes may be affected when the influence of acquired immunity is better understood, and there is a definite need for more field studies of its role. Mathematical models of epidemiological and control processes, for the purpose of planning control strategy and calculating costs and benefits, will also be markedly influenced by consideration of acquired immunity.

Mathematical models

No discussion of the epidemiology of schistosomiasis can be made without some appreciation of the development of mathematical models of transmission and of their predictive value to epidemiologists and those responsible for control strategies. Since the outstanding work of MacDonald (1965) there have been further attempts to develop models of the entire transmission cycle. These have generally been too broad and in some cases are

based upon faulty premises and inadequate data. It is of interest to note that Nasell (1975) has obtained results, which support MacDonald's conclusions in terms of the existence of a 'break point' in transmission and concerning the relative efficiency of various methods of control, which were based upon computer simulations and which necessitated the allocation of numerical values to the parameters of his model. MacDonald claimed that his conclusions held regardless of the numerical values which were used in the simulation. This claim is now supported by the results obtained from Nasell's model.

A study group (Hoffman, 1975) recently concluded, however, that there is a need for mathematical or computer modelling of specific sub-systems aimed at establishing biologically sound models including : effects of reducing water contamination ; effects of miracidial reduction on cercarial output ; effects of snail reduction on cercarial output ; effects of cercarial reduction on infection ; effects of selective treatment programmes on cercarial output ; and the relationship between environment, infection and disease at population level.

Mathematical models are being increasingly used in the analysis of systems and their response to variable inputs. These models are being developed for schistosome infections and for natural snail populations and may be adjusted to real situations and used to predict the outcome of deliberate modifications (WHO, 1973). Computer programmes which have been developed on an experimental basis may lead to considerable improvement in the objective evaluation of alternative control measures and are already proving valuable in the detailed design of mollusciciding programmes. The development of such models is clearly

desirable but their limitations and the inadequacy of available data must be considered.

Economic importance

During the past 20 years, despite the substantial advances which have been made in our knowledge of schistosomiasis, attempts to control the disease have been, with certain notable exceptions, limited in scale. This is attributable, in part, to the inadequacy of control tools for large-scale use and in part to the failure to realise earlier, the public health importance of schistosomiasis and therefore to accord it appropriate priority in public health programmes. It is vitally important to establish the relative importance of schistosomiasis to other health problems of an endemic area and measure the impact of the problem on the community as a basis for estimating disability in economic terms. In many endemic areas such analyses are essential to public health planning and to the rational allocation of resources for this purpose. While it has been recognised for some time that certain parasitic diseases may constitute a serious economic burden in developing countries, the attempts made so far to measure their economic significance and the economic benefits which might accrue as the result of their control have been generally inadequate and of doubtful practical use for planning purposes (Olivier, 1974). The economic assessment approach may not be applicable to all aspects of the public health field, where other pertinent factors may be considered, but its value in support of decision making must be appreciated. There are many workers, however, who consider that this may be attempting to measure the immeasurable and who are equally convinced that there is sufficient evidence of disease and social consequences caused by schistosomiasis in many

endemic areas to warrant the implementation of control measures and justify the requisite resources to support them.

Methods of control

It is generally agreed that a combination of methods directed against different links in the life-cycle is most likely to achieve clear and most rapid control, but the composition of any control programme will necessarily vary in the emphasis placed upon one or more different approaches according to local conditions, the goal of the control effort, available resources and a feasible strategy. There are situations however where funds are limited and a large measure of worthwhile benefit could be obtained by applying a single control approach which must be determined in relation to local epidemiological considerations.

Snail control is a rapid and effective means of reducing transmission and its efficiency is likely to be enhanced if combined with other methods of control (MacDonald, 1965). There are now very effective molluscicides available for control of the molluscan hosts of human schistosomes and substantial and scientifically acceptable data are available that show the impact on 'incidence' of infection achieved in different control programmes in Ghana, Tanzania, Egypt and Japan. In other countries where changes in prevalence were estimated, marked reductions were observed in Brazil and in Rhodesia. Examples of successful control schemes in which combined mollusciciding and chemotherapy have been used include those in the Fayoum Governorate of Egypt, in Tanzania, West Cameroon, Iran and Rhodesia. The outstanding control programmes in Japan and Venezuela have combined chemotherapy, mollusciciding, environmental control, sanitation, health education and legislative action. In each

of these countries the programme has resulted in a marked reduction in schistosomiasis as a problem of public health significance (WHO, 1973).

It is now considered that mollusciciding is most cost-effective where the volume of water to be treated per person at risk is small. It is therefore well suited to arid areas where transmission is seasonal and confined to a few small habitats. It may be unsuitable however in large rivers and lakes unless transmission is focal in distribution along the periphery. Mollusciciding may be suitable where the population density is high, and the water volume per person is therefore low, although the total water volume may be large. Irrigation schemes where water management is controlled are also well suited to chemical control.

More adequate strategies and delivery systems are however required to optimize the cost-effectiveness of mollusciciding, which will necessarily vary in different habitats. There is a need to explore the potential of new formulations of available compounds, such as slow release and bait mechanisms, and to examine the possibilities of developing molluscicides from natural products of local origin in endemic countries. Costs of molluscicides are high, usually requiring much needed foreign exchange, and the possibilities of local manufacture of even the more sophisticated compounds must be examined.

Habitat modifications

In many habitats the application of molluscicides results in only a temporary reduction of the snail population and a temporary reduction in transmission. The available tools and regimens therefore call for sustained measures requiring competent direction, trained manpower and considerable recurrent expenditures. These

cannot always be justified or sustained on economic grounds and careful consideration must therefore be given to developing different or complementary types of control including biological methods and the reduction or control of snail habitats by environmental changes and engineering means. Bradley & Webbe (1978) have recently considered the advantages of such an approach and the reasons why attention is now being focussed upon them. These include: the fact that their effect is persistent without continual re-application; recurrent costs are often lower than for other methods; health benefits may extend to other infective diseases; benefits outside the field of health may sometimes accrue, as in increased agricultural production; evidence of success in controlled epidemiological studies has accumulated; labour and funds are more interchangeable than in mollusciciding or chemotherapeutic programmes; the approach lends itself to local or small-scale use; and environmental concern has made people unenthusiastic about chemical control! According to such data as are available the prevalence of *S. japonicum* in mainland China has been greatly reduced by various control approaches including destruction of snail habitats by labour intensive methods at low capital cost, wide adoption of an improved system of faecal processing and intensive treatment of infected individuals. Detailed epidemiological evidence is however scanty.

Chemotherapy

During the last ten years developments in the chemotherapy of schistosomiasis have advanced to a stage where it is now seriously thought that it may be used on a large scale in control programmes. Through wider application, chemotherapy may play a role in reducing not only the

severity of the disease but also the rate of transmission. The predicted prospects for successful large-scale use of schistosomicidal compounds are apparently lowest for *S. japonicum* and highest for *S. haematobium* at this time (WHO, 1973). There is a need however to develop new drugs of several kinds. New drugs are needed for mass treatment of *S. mansoni* and *S. haematobium*, or existing compounds should be modified to eliminate undesirable side effects. Prophylactic and repository prophylactic drugs should be developed for each species of schistosome — a recent study group (Hoffman, 1975) considered that this is particularly important for long-term control prospects if the present attempts to develop vaccines are unsuccessful. A suitable drug for mass therapy of *S. japonicum* is also obviously desirable. It is now considered that future long-term development of drugs may be based on detailed knowledge of the development, biochemistry and physiology of schistosomes — hopefully identifying potential targets for chemical attack such as unusual enzymes or unique but critical metabolic paths or growth requirements (Hoffman, 1975).

Reduction of water contact and contamination

A major component of the economic progress of so many developing countries is the installation of irrigation schemes and frequently the creation of lakes and dams to store water and produce hydro-electric power. In considering the overall problem of schistosomiasis control in relation to man-made transmission, it is important to remember that the definitive host, man, is the true vector of the parasite by contaminating the aquatic environment in which he acquires the infection from the snail intermediate hosts. Human ecology must therefore receive appropriate

attention in any considered long-term measures for control of transmission. It is clear that in many situations the spread of transmission or a reduction in its intensity will depend upon integrated control measures, including sanitary engineering and health education and the provision of clean water supplies for domestic and recreational purposes, in order to minimise the contacts between man and potentially dangerous waters. Many factors will of course influence the decision to introduce such facilities, which generally require high initial capital funding. Such a scheme may however have a strong appeal to public health administrators as part of a broad rationale of public health control in which schistosomiasis is one of several problems, but not necessarily of the highest priority. Every attempt should be made to link schistosomiasis control with a general improvement of the environment and to complement rather than compete with other specific health programmes. It is however conceivable that, focally, the application of combined measures involving available molluscicides and chemotherapy may play an important role in many of these situations now, and authorities should be encouraged to attempt such work whenever feasible. Schistosomiasis may affect a development programme adversely and these negative effects may be reduced by designing the scheme to minimise transmission of schistosomiasis and by making financial provision for recurrent costs of control measures and unforeseen problems in the budget of any water development project.

Development of vaccine

Present knowledge of the mechanism of the human response to schistosome infection is inadequate to guarantee success in efforts to develop a vaccine.

Many people however seriously doubt that schistosomiasis will ever be effectively controlled without a vaccine, except in limited areas. As already stated, no direct evidence exists that man develops immunity to schistosomiasis but partial immunity has been demonstrated in various animals, including primates. Enormous resources are currently being applied to studies of immunity and immunology with the aim of developing a vaccine against schistosomiasis and this should be regarded as a worthwhile long-term investment in the development of a future control tool. It should not however in any way be confused with the allocation of resources for control efforts which can be initiated now with available tools in short or medium term time-scales, and which may achieve predictable goals and confer considerable much-needed benefits.

Future control strategy

At the 28th World Health Assembly this year a resolution was adopted requesting the Director-General to initiate a study of the problem of schistosomiasis with a view to drawing up a strategic framework on a global basis for the prevention and control of the disease — which it was stated is one of the most widespread parasitic infections of man and which is second only to malaria in public health and socio-economic significance.

The development of a global control strategy or even effective control on a more restricted basis is a formidable and expensive task. It will call for long-term planning and decisions on overall strategy which include : establishing criteria for selecting target areas and consideration of the applicability of currently available control methods to them ; the adequacy of financial and man-power resources and, probably most important, the identification of interest and motivation by national

governments (Hoffman, 1975). There must be clear realisation on the part of those undertaking control measures that a long-term time-scale of sustained effort and, therefore, recurrent expenditure will be involved. It is also essential that control measures are clearly identified which will result in effective control and achieve predictable goals over short, medium and long-term periods. Snail control and chemotherapy are available to us now, but the development of habitat control by environmental changes and engineering means may involve medium or long-term planning and execution, as will the acceptance and use of alternative water supplies and environmental sanitation coupled with health education in many places. Those who consider that raising the standard of rural health services is a panacea for achieving control of this problem and related ones should remember that schistosomiasis transmission is characterised by its variability and complexity and requires specific control inputs to achieve particular results. Nevertheless available tools cannot be effectively used unless a minimum basic health infra-structure exists in the operational area, and probably one of the greatest constraints to the progress of control in many situations will be the lack of capability to accept and apply advanced technology in the short term even when adequate resources are available. The adequacy of manpower resources, particularly with managerial skills, poses a serious problem and training programmes must be developed in new pilot schemes and existing control programmes. It is essential that basic research is also continued and adequately supported to assess the impact of the problem ; to improve the cost-effectiveness of available control tools and delivery systems and establish new ones ; to discover new drugs, and in this area industry has a key role to play ;

and to conduct long-term studies towards developing a vaccine.

The provision of adequate financial resources to carry out the initial phases of control on a large-scale will call for funding far beyond that which many individual governments can provide and aid from bilateral and multilateral donors must be properly integrated with national health budgets in order to initiate new control programmes and expand existing ones where appropriate. It is vitally important that every effort is made to reduce the costs of control measures and that these are eventually transferred to national government responsibility for long-term maintenance purposes.

International agencies involved in water resources developments are now generally aware of the dangers of exacerbating levels of transmission and the need to consider the problem at the planning

stage. The cost of current control programmes varies considerably (a range of US \$ 0.40-12.00 per capita has been given — WHO, 1973) but it is generally higher than many poor countries with widespread endemic schistosomiasis can afford in terms of generalised transmission control schemes. Schistosomiasis control is however believed to be within the capability of some countries that do not have programmes and it is considered that a high degree of effective schistosomiasis control is financially feasible in all commercial irrigation schemes (WHO, 1973).

Under the umbrella of the United Nations family of agencies I think that the necessary planning and coordination of efforts for large-scale operations can take place and that ultimate progress will be made towards lasting effective control of the problem.

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MAN-MADE LAKES AND SCHISTOSOMIASIS

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One of the tragedies of modern technological change is that, however well intended, many of the effects and unintended byproducts of ecological impact seem beyond our present capacity to predict or to control. As massive land and water developmental projects become more sweeping and are scaled up to care for the needs of larger and more rapidly burgeoning populations, the unexpected and the unpredictable aspects increase at the same or even at a higher rate than does the scale of the projects themselves. A few years ago no one could have predicted what the automobile would do to the air we breathe or how the sheer impact of human numbers, tied to increasing expectations for material goods and services, would affect the pattern of our lives or the rights of our children to enjoy similar privileges. I was shocked to read recently (*Sierra Club Bulletin*, October 1975) that the energy consumed by the American people since 1960 exceeds the total estimated energy consumption of the entire human race prior to that time.

The scale of our technological and energy-demanding activities not only dwarfs anything ever known before, but the impact is of such an order of magnitude as to require a wholly different approach to its understanding — and to its control. Among these technological developments, the electricity-producing, water-controlling high dams have been the

epitome of progress and of mastery over the forces of nature. And, in fact, they are. But with their very immensity, their boggling complexity, and their vast impact on the land and its waters, comes an equal enlargement of the accidental, the unintended, and the unforeseen. We speak rather glibly of the need for multidisciplinary input in the planning of such great structures but, in fact, the design and planning of these enormous dams has in all countries largely been handled as a straight engineering problem, once the cost-accounting justification has been made (generally by the engineers). Cost-accounting therefore usually means only the industrial and economic justification, to which public health and sociocultural factors may subsequently be appended, too often as an afterthought. This has certainly been true in the past in the U.S., until a few years ago when the environmental movement became a political reality.

In part, this reflects the priorities that we all have been trained to accept: First, Can the dam be built? Second, Should the dam be built? Third, [given (1) and (2)], What ecologic or humanitarian or health trade-offs against the project are fiscally acceptable or politically tolerable? The first challenge, in any case, is to build the dam, to «conquer» nature. Our responsibility to the voiceless people whose ancestral lands and artifacts

and homes are to be inundated, or to the animal and plant associations that will be destroyed are far less compelling — at first, though not necessarily later. Engineering simplification is, of course, necessary to get the job done, however complex the natural or social conditions may be in which the project is to be undertaken. And that engineering outlook, with its pragmatic, technologically constrained visual focus, is perhaps the one least amenable to the conflicting, confusing, and sometimes nonscientific claims related to sociocultural and biological priorities.

This is the context in which I would like to discuss briefly some of the «after-thought problems», problems thought about after the dam and the lake, after the impact, good and bad. They are chiefly public health questions, specifically, schistosomiasis, in keeping with the purpose of this conference. In Africa, the giant engineering projects for water control are designed to prevent «loss» of unused water (still a controversial concept), to permit perennial irrigation for multiple cropping, maintain water-level constancy for flood and drought prevention and for navigation, and to maximize the water head for huge electrical power generation for new industries and urban use. Not mentioned in most reviews of such projects are the relative well being and the health of those displaced, their social or tribal continuity, or the increasingly wide-ranging effects that altering the face of the land and its patterns of water flow has on the ecological balance, soils, plants and animals, and residents both local and hundreds of miles away. A sequence of priorities based on engineering «realities» such as have been universally followed in the past may still prove to be necessary, even in future planning, as the political, social,

and economic pressure on all governments is to do **something**, to demonstrate dramatically the capacity to lead and to solve the problems of a huge, growing and often impoverished population. In fact, not to go ahead with such projects as the Volta, the Kainje, Kariba, or Aswan High dam could take far more wisdom and courage than any of us has a right to expect. Probably every individual in attendance at this conference was fully aware years ago of the high probability that schistosomiasis would eventually appear among the evacuees or new residents of the major water control projects in schistosome-endemic areas of Africa or in areas that could become infected, such as Lake Nasser. Many of these public health warnings were disregarded in favor of more pressing priorities. The real responsibility of this conference, it seems to me, is not to cry «I told you so», however professionally couched, or try to explain away evidence of schistosomiasis spread that only recently has become generally recognized. Rather, it is for us to take positive steps to insure that, somehow, the importance of public health aspects and consideration of human values become a necessary part of the planning process leading to a preliminary socioeconomic cost/benefit (or damage/benefit) investigation preceding any future project or area development. The method must be an agreed-upon, standardized and involuntary one if it is to succeed. No testimonial on our part here of the importance of this planning will have much effect on cost/benefit determinations by non health-oriented planners, however expert in their own field, without it being an obligatory and publicly accepted procedure. An obvious stimulus would be to make international funding contingent upon such prior planning.

Each of the past major projects in Africa has represented an enormous international effort. Whatever the specific purpose or intent of the project, each has also affected and therefore is to some degree responsible for and to the entire living community in which it is found. An official and public sense of responsibility for effects on the local population has to become a major element in the planning process if health-protective measures are to have any chance to succeed.

Man-made Lakes in Africa

The world's largest man-made lakes are in Africa — a reflection of the enormous river systems of the continent, the relatively flat topography in which the lakes lie, and the size and importance of the effort involved in damming the rivers and creating the lakes. Surely the figures are familiar to us by now: The Aswan High dam, 17 times the mass of the Cheops pyramid, a kilometer-deep rock-fill built like an enormous truncated pyramid, with 6 house-sized water intakes into 12 giant turbines, each planned to generate almost a billion kilowatts of power. Of Lake Nasser behind it, we have all heard it represents: 170 billion (million) cubic meters of water when it becomes filled, which has been announced as occurring during the time of this conference, when its 200-mile length will cover 7,000 km² (1800 square miles), to a maximum depth of about 170 m, and a total shoreline that is said to exceed that of the Mediterranean and Red Seas combined. Some 120,000 Nubians have been displaced by the lake, 60,000 Egyptians moved to Kom Ombo, and 60,000 Sudanese to the Atbara River area.

The Kariba dam on the Zambesi between Zambia and Rhodesia has comparably impressive figures. It has been fully filled since 1963, forming a lake

5,250 km². Owing to its earlier completion, Lake Kariba is better studied with respect to disease epidemiology and human evacuation and resettlement problems, the latter chiefly from the pioneering work of Thayer Scudder and Elizabeth Colson, who have observed the Kariba basin relocation problems among the Tonga peoples since 1956, making more than 10 separate trips.

The Volta dam in Ghana on the Volta river has created the giant of all man-made lakes: Lake Volta, 9,000 km² (3275 square miles); 70 m maximum depth; 80,000 persons displaced, and a major fisheries industry developed at a town of 80,000 replacement immigrants. Some 60,000 tons of fish were landed in 1968.

Nearby is the smaller but still significant Kainji dam creating the 1,500 km² Lake Kainji on the Niger river in Nigeria, completed in 1968.

Other large dams are the Kafue in Zambia, the Cabora Basso in Mozambique, the Tafilalet dam in Morocco, and the Zaire (Congo) River dam at Inga in Zaire (the latter river flows with up to 10 times the maximum flow rate of the Nile, or 75,000 cu m/sec). The Sudan has 2 economically and medically important reservoirs on the Blue Nile, which are responsible for the Gezira irrigation region that lies between the 2 approaching main branches of the Nile: the Sennar reservoir, 54 sq. mi., completed in 1925, and the newer Roseires reservoir, 75 sq. mi., completed about 1967 — and both are important centers of schistosome transmission.

Together, almost 8,000 sq. mi. of land has been flooded in the first 4 of these projects, and 300,000 residents have been evacuated and relocated. To this, one could add 150,000 persons to be displaced by the Hadejia valley project near Kano,

northern Nigeria, and 120,000 already displaced by Lake Kossou in the Bandama valley of Ivory Coast. Lake Victoria, too, is now considered a dammed lake because of the Jinja dam at its outlet, which has raised the water level to expose the full 70,000 km² of its surface, creating new foci for schistosomiasis transmission (Webbe, *In* : Miller, 1972).

These are vast changes brought to the landscape of the continent and to the people on it — and schistosome flukes have been brought by man to each of these projects ; and, in each, resident or newly arrived appropriate snail hosts soon appeared to complete the cycle and establish vastly increased spread of human disease, particularly in the 8-15 year age range. Similarly, in dozens of smaller dams and thousands of miles of primary and secondary feeder and drainage canals associated with the impounded waters, schistosomiasis followed.

An accurate survey of the status of schistosomiasis in the man-made lakes of Africa simply has not been done. Lack of reliable or sufficient information on the existence and spread of disease has been a primary block to any effective wide-scale control efforts. Numerous discussions — such as this one — at conferences or symposia — such as this one — decry the tragedy of schistosomiasis and the seemingly inevitable tie — in between water for irrigation and water for schistosomiasis transmission. But the hard data on which action must be based are still lacking, and we are forced to make broad assumptions and then extensions of conclusions based upon isolated and small samplings. Waddy's 1975 report gives the most recent account, in part based on his practical experience as a UN health officer at the Kossou dam in Ivory Coast, and as the former Chief of the

Ghana Medical Field Units. The UN Development Program (a cosponsor of this conference) financed studies at lakes Nasser, Kainji, Kariba, Volta, and Victoria ; chiefly limnological and fisheries studies, however, rather than disease investigations. A WHO Inter-regional Schistosomiasis Research Project, based on Lake Volta, also undertook some studies at Lake Nasser. Both the Lake Kainji and Nasser projects were ended in 1974. The Lake Volta schistosomiasis project continues actively. A significant new study, an ambitious ecological investigation of an entire dam-lake-and river basin, is the current 3-year \$1 million study of the Aswan High Dam and its impact on the associated river basin. This program, still in its first year, will involve a number of aquatic biologists and other specialists. The project is conducted by the Egyptian Academy of Scientific Research and Technology and the University of Michigan, funded by the US Environmental Protection Agency and the Ford Foundation. We congratulate the participants and the governments concerned for recognizing and implementing this desperately needed pioneering investigation. We can also hope that it will serve as a prototype for studies of other water basins, preferably before a dam or irrigation system is built or even contemplated. Short of completion of this study, we have only brief accounts of active schistosomiasis transmission and the presence of vector snails, but it still is enough to establish that transmission is now occurring in all of the major man-made bodies of water in Africa. These reports include a series of papers on schistosomiasis transmission in Lake Volta by I. Paperna (1968, 1969, 1970) ; and various WHO mimeographed reports (Dazo & Biles, 1972a, b, 1973 ; Jobin, 1973 ; Jones, 1973 ; Noamesi & Morcos, 1974 ; Scott & Chu, 1974a, b ; Teesdale, 1971). A valuable WHO mimeo-

graphed bibliography of about 500 references on «Water Resource Development and Public Health» has just been issued (MPD/75.4), prepared by Bernard-Kirukhine and Deom of the Division of Malaria and other Parasitic Diseases of WHO. Webbe at the New Orleans Conference in 1972 (In : Miller, 1972) summarized our meager knowledge of the status of transmission in the major man-made lakes as of 1971. Both schistosomes are in Lake Kariba at limited foci where the snails *Bulinus (Physopsis) africanus* and *Biomphalaria pfeifferi* are associated with mats of the water fern *Salvinia auriculata*. In 1968 (10 years after completion of the dam), prevalence of *S. mansoni* was 16% overall, and *S. haematobium* occurred in 1967-68 on the shores of Lake Volta among fishing communities near the water weed *Ceratophyllum*, which was heavily populated with *Bulinus truncatus rohlfsi*. Along the Afran shore area, 90% of the children under 15 were infected. (*B. pfeifferi* has not yet been reported from Lake Volta). The complex epidemiology of transmission in the new fishing villages along Lake Volta still requires intensive study.

In Lake Kainji both snail hosts are present and human infection has fluctuated in the newly settled lakeside communities (31% for *S. haematobium*, 1.8% for *S. mansoni* in 1970). In fact, it has proven to be less severe than was predicted — attesting to the individuality of each focus of transmission.

S. haematobium occurs very commonly among the Lake Nasser fishermen (approximately 60%) and probably has been spread to the abundant *Bulinus truncatus* around the lakeshore, particularly since the fishermen live in their boats, for fear of snakes and scorpions along the shore. No species of *Biomphalaria* has yet been found in Lake Nasser, though

once the water level is stabilized, the likelihood of snail survival there is probably good, in spite of *Bulinus* mass die-offs on the shore due to heat and draw-downs. To quote Webbe (In : Miller, 1972) : «The available evidence from the man-made lakes in Africa manifestly shows that transmission of schistosomiasis is occurring in the body of every major lake, and in related irrigation systems».

New and increased levels of transmission in endemic regions have always rapidly followed resettlement of human populations and new irrigation channelling. There may be only a very few infected individuals initially, even among the immigrants, yet the rapid spread of infection to others, especially to adolescents, seems to follow inevitably. Numerous examples of the speed of transmission have been described, frequently going from 0-5% in a population to 50-80% in a year or two, often involving all of the children within a new community in a short period. Such changes are currently being followed by the NAMRU-3 Parasitology Department in the Luxor area.

Outside Africa, in endemic areas, much the same situation is found. In Brazil, projects in the Sao Francisco Valley of northeastern Brazil certainly will increase the danger of infection among these malnourished, hyperparasitised and impoverished people.

The talk of damming the Mekong, with cost estimates running up to 23 billion dollars, has died down following events of the past 2 years in Southeast Asia. But the potential remains — and the result would be the most extensive ecological and human disruption yet attempted, in one of the most intensively cultivated and highly populated areas in the world. Newly discovered foci of *S. japonicum* (or a close relative) are very

much a part of this epidemiological picture. As an illustration on a relatively small scale, the disease impact of creating the Ubolratana Dam in Khon Kaen Province of Northeast Thailand was recently discussed by Chamlong Harinasuta (1975).

It is virtually impossible for any single nation, especially countries in greatest need for these projects, to anticipate and build into a water-control project the means to prevent unwanted ecological or epidemiological ramifications of high dam construction and man-made lakes, especially since only now are we beginning to recognize them. A multifaceted international team of experts, specialists in the regions' epidemiology and sociocultural characteristics, with internationally-backed financial support and strong public opinion behind it, should be part of each initial feasibility study, focusing on the other side of the dam, on the environmental aspects of the project: i.e.: a determination of the biological, epidemiological, public health, and sociocultural effects that may develop and must be anticipated. The report and recommendations of this team, should then become part of each project's initial cost-benefit formula for project justification, as much as part of the plan as the geological stress calculations for support of the dam: i.e., a social and health stress estimate. We presently lack the quantitative methodologies or sufficient computer-banked data for more than a reasonable guess as to whether — or when — a disease is likely to appear under a given set of conditions. Yet much has been learned from the experience recorded so far. And we can be reasonably certain that if the physico-chemical and limnological conditions are suitable, vector, snails will be introduced, infected humans will appear, contamination of the water

with infected feces or urine will occur, and schistosomiasis will follow. The level of infection and the speed of spread obviously are contingent on many factors, such as snail population size (often related to aquatic weed growth), the starting infection level in the human population, human customs and sanitary habits, degree and frequency of water contact (especially by adolescent children), the strain of parasite and snail host. We do know enough of the epidemiological factors to develop a reasonable prognosis of water-borne disease probabilities and to make similar educated guesses on other sociocultural parameters of importance to the well-being of the population affected. Estimates on the social impact, avoidance of relocation stress, preservation of community or tribal organization and continuity of leadership must come from other specialists.

During the early phases of planning and cost allocation, it is relatively easy to include reasonable sums for the strengthening of community health and for high-priority efforts to protect the social organization and culture of affected community or tribal groups. Costs of these essential — and difficult — activities to protect the social integrity of the groups to be flooded out and relocated can nonetheless be incorporated relatively easily into the multimillion dollar general plan. But after the plan is funded and construction has begun, if public health costs then must be added on, they will significantly increase costs of resettlement, as the trauma induced by relocation of villages (or the threat of it to unprepared occupants) will seriously affect the health and morale of the people to be relocated. Any health or relocation plans made after construction of the dam begins are too late. This is especially true in prevention of bilharzia spread, as has been demon-

strated over and over again in Africa and the Middle East.

Protection of people is not cheap, but it is far less costly than cement and earth-movers. Planning for protection of health and social values deserves far more financial support, expertise, and public acceptance than they have been allotted so far in the scramble for international funding. The lesson seems inescapable at this point: prevention is cheaper than cure, whatever the cost, even if we cannot be certain of success. I suspect that funding that is finally brought up to the level required for suitable health services and the popular acceptance of this as a necessary investment in people, would go a very long way toward controlling the rampant outbreaks of disease, malnutrition, and social dissolution that has accompanied nearly every relocation of large numbers of people dislocated by flooding of their lands. For this reason, I would like to suggest that we recommend at this International Conference that international financial support for any project be tied to acceptance of the cost of health maintenance as an integral part of the basic project cost. The revolutionary effect in recent years of obligatory «Environmental Impact Reports» that must precede any federal funding in the U.S.A. is an example of how this can operate. A required «Health and Social Impact Report», as recommended here, could exert a major balancing effect that for the first time might place public health and sociocultural values on a par with engineering, agricultural, and industrialization objectives that are incorporated in the planning and justification of each internationally-funded major developmental project. Perhaps this can help bridge the gulf that presently lies between the environmentalist-health scientist and the engineering technologist, as repre-

sented by the following poetic laments by Kenneth Boulding:

First,

A Conservationist's Lament

«The world is finite, resources are scarce,
Things are bad and will be worse.
Coal is burned and gas exploded,
Forests cut and soils eroded.
Wells are dry and air's polluted,
Dust is blowing, trees uprooted.
Oil is going, ores depleted.
Drains receive what is excreted.
Land is sinking, seas are rising,
Man is far too enterprising.
Fire will rage with Man to fan it,
Soon we'll have a plundered planet.
People breed like fertile rabbits,
People have disgusting habits.»

Moral:

The evolutionary plan
Went astray by evolving Man.

But, we have:

The Technologist's Reply

Man's potential is quite terrific,
You can't go back to the Neolithic.
The cream is there for us to skim it,
Knowledge is power, and the sky's the limit.
Every mouth has hands to feed it,
Food is found when people need it.
All we need is found in granite
Once we have the men to plan it.
Yeast and algae give us meat,
Soil is almost obsolete.
Men can grow to pastures greener
Till all the earth is Pasadena

Moral:

Man's a nuisance, Man's a crackpot,
But only Man can hit the jackpot.

It has been estimated that only about 10% of the potential sites for irrigation and waterpower have been tapped, although the most readily and economically feasible ones clearly already have been. Whatever new dams and lakes are still to be created from this massive potential, the possibilities for disease and human disruption are equally evident. Unless we establish new approaches and new understanding promptly and see that they are fully acted upon, we (to paraphrase Santayana) will join those who, by ignorance of history, were doomed to repeat it.

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Chairman's concluding note

**EPIDEMIOLOGY, SOCIO-ECONOMIC ASPECTS AND CONTROL
OF SCHISTOSOMIASIS, SOME KEY QUESTIONS**

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Our speakers have viewed a wide scene. We have had much information, some speculation, some suggestions, and a great deal of wisdom. I shall not try to cover the waterfront, but perhaps before closing I might focus your attention on some of the issues, some of the questions that we need to worry at between all the good things that have been provided for us by the organising committee.

What are the big questions? What are they in epidemiology? If we consider first the hard-line traditional epidemiology, are there questions still unsolved or which someone may have answered and be able to tell us about here?

1. What is the role of immunity in human schistosomiasis? Not an abstract or academic question, and not an easy one. Several workers have attempted to solve this question from observational data, including myself. It is hard to deny that immunity to *Schistosoma haematobium* occurs in man, but all the studies are open to criticism by the determined sceptic and none is decisive about mechanisms or types of human resistance to infection. This is not an academic question because it affects strategies of control. If immunity is of importance, the sort of issues involved in stable versus un-

stable malaria are applicable to control programmes for schistosomiasis. The issues would be of particular relevance to attempts at 'partial' control and 'self-help' approaches — if immunity is important in the community then the outlook for 'self-help' efforts is very bleak and the search for a vaccine becomes the preferable strategy.

2. What is the epidemiological relation of infection levels to disease in communities? Again this is not an easy question but is practically important. If we can push down intensities of infection by practicable control means, how far does this solve the real health problems?
3. Relating these two questions, how do intensity, immunity, and pathological consequences inter-relate? Would the sort of intervention recommended by Kloetzel, of the Faculty of Medicine at Jundiai, Brazil, whereby there is selective chemotherapy near the time at which immune processes may become effective, reduce disease due to *S. mansoni* greatly in places where transmission cannot be interrupted?
4. A question that Dr. Willard Wright, formerly of the National Institutes of Health Bethesda, Maryland, would

have raised, had he been here, would have concerned schistosomiasis in south-east Asia. Currently *Schistosoma japonicum* or an *S. japonicum*-like schistosome has been reported from the human population in Laos, Cambodia and Thailand. Yet *Oncomelania* snails are said to be absent from the entire region. Furthermore, investigators have been unable to infect any *Oncomelania* vector of *Schistosoma japonicum* with miracidia hatched from eggs of the parasite from patients in these countries. The only molluscan intermediate host thus far demonstrated has been the hydrobiid snail *Lithoglyphosis aperta* from Khong Island in Laos. The dog has been the only lower animal found infected in the countries in question. The vast water development programme for the entire Mekong River Basin is already under way and constitutes a considerable threat for the spread of the disease in this region. The further elucidation of the transmission cycle of the parasite is a matter of some urgency.

5. Even where the epidemiology of schistosomiasis is known in general terms, it must be made local and particular, in enough detail to carry the control programme tactics we aim at. Generalities are of limited use in control work, as may be illustrated from malaria experience. The very methods of water management that were so effective in keeping down malaria in the Tennessee Valley Authority's reservoirs would have actually increased the density of malaria vectors had they been applied — as was once briefly suggested, — to Volta Lake in Ghana.

6. There is great enthusiasm at present for self-help approaches to schistosome control at the village level, as Dr. Mahler, the Director General of the WHO, has indicated, and the use of auxiliaries on a larger scale in place of medical men on a small one. One can see that this is essential if coverage is to be achieved, and local self-help is clearly an excellent thing, but epidemiological support for tactical control decisions within that strategy is weak. Small may be beautiful; it also needs to be effective and that usually requires more rather than less refined epidemiological understanding than do cruder large-scale methods.

7. Dr. Stockard, of US AID, has drawn attention to economic aspects. The medical men must provide data of the sort that economists can use. But the economists must take a wider view. Cost-benefit analyses are of great usefulness. Economists are skilled at including hidden costs. They are perhaps less able to include all the benefits. I was recently told that a major aircraft went out of production because it was shown that it needed one more seat full crossing the Atlantic than did its rival, to break even. Also that the calculations omitted to consider that the wings of the discarded model outlasted those of its rival three times over and that because it was such a quiet aeroplane it was always much fuller in any case. This is clearly bad economics, but in health costing it is very difficult indeed to decide what is to be included, and how to measure. If we consider, along with Dr. Tolba, of the United Nations Environment Programme, Nairobi, quality of life then, we must either write that quality in dollars, or get the control costs transformed to the

same terms as quality of life, or at least express the competing budgets against schistosome control in terms of their effects on quality of life. I see no easy solution to this problem.

8. The last group of major epidemiological or social questions concern human behaviour change : 'motivation' as Dr. Mahler put it. I do not know how far this is a matter of science and in my introduction I have pointed out the rather poor record of health education of a traditional sort. But certainly any swing towards ecological, environmental and sanitary approaches to schistosome control is more demanding on the community

than molluscicide or even chemotherapy. Motivation can often substitute for money. If it is to be a prerequisite for schistosome control methods, then very profound changes have to take place in many communities before effective control can occur. Here the formulation of the key questions is as yet unclear, as well as the answers.

I hope in this plenary session we have been able to review progress in the epidemiological and socio-economic fields, and also to provide some new and unanswered questions for your consideration. I thank you on behalf of all the speakers for your attention and declare the session adjourned.

SUBCOMMITTEE SESSIONS

SCHISTOSOMIASIS AND AGRICULTURAL LABOR PRODUCTIVITY

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An earlier study (Weisbrod et al., 1973 ; Baldwin & Weisbrod, 1974) sought to assess the quantitative impact of *Schistosomiasis mansoni* on various measures of labor productivity in St. Lucia, West Indies, during the period 1966-68. The present paper utilizes newly available productivity data from 1969-71, three years after the original study, to test the hypothesis that the debilitating effects of schistosomiasis increase with the duration of infection.

The methodology employed involves comparing (a) the labor supply (amount of time worked), as well as (b) the labor productivity of workers who are similar except in conditions of health. Specifically, we examined 4 hypotheses ; hypothesis 1 : schistosomiasis reduces weekly earnings. This was tested by examining the relationship between earnings per week and the presence of schistosomiasis infection, holding constant a number of variables reflecting the presence of other diseases and specified personal characteristics such as age and sex. Hypothesis 2 : schistosomiasis causes workers to shift to physically less demanding jobs. This was tested by examining the ratio of days worked at «task» jobs to total days worked, for workers who were and were not infected

with schistosomiasis, again controlling for other diseases and personal characteristics. This ratio was used to reflect the view that task work — including such work as digging drainage canals and carrying bananas from the field — is more difficult than day work ; hence, it is expected that infected workers will do relatively less task work. Hypothesis 3 : schistosomiasis reduces productivity per day, was tested by regressing earnings per day on the independent disease and personal variables. Finally, hypothesis 4 : schistosomiasis reduces the amount of labor time supplied per week, was tested by regressing days worked per week on the independent variables. If our hypothesis is correct that schistosomiasis exerts an increasingly adverse effect as the duration of infection increases, then we should find larger and more statistically significant coefficients for the schistosomiasis variable using our newer data than we found previously.

In our earlier regression analysis, no statistically significant relation was found between a worker's earnings per week and whether the worker was or was not infected by schistosomiasis. The estimated impact of schistosomiasis for males in the earlier study was to reduce weekly

* Financial support was provided by the Rockefeller Foundation. An expanded version of this paper, under the title «Parasitic diseases and agricultural labor productivity», is to appear in a forthcoming issue of *Economic Development and Cultural Change*.

earnings slightly, but the reduction was not statistically significant. Three years later, the time to which our follow-up data apply, the coefficient is again found to be not significantly different from zero. In short, we found no evidence that the severity of schistosomiasis is having an increasing effect on weekly earnings.

Working at certain «tasks», such as digging drainage canals, is physically more demanding than «day» work, but it is possible to earn considerably more on a task job. Thus, if workers were debilitated by disease we might expect them to prefer the easier, day work. As a result, «healthy» workers and «ill» workers could be distinguished by the relative amounts of day versus task work they do.

To test the hypothesis that infected workers adjust to debility by choosing easier work, we estimated a regression equation of the proportion of task days to total days worked for each worker, on the same independent variables used to test the weekly earnings hypothesis. Schistosomiasis did not exert a significant effect in either the original or the follow-up study.

If schistosomiasis causes debility among workers, we would expect workers' marginal productivity to be reduced. Insofar as marginal productivity may be proxied by earnings, we can test the hypothesis that schistosomiasis cuts labor productivity by testing its effect on earnings per day worked. This would be a test of the effect of the parasite on potential labor productivity, whereas our previous test, of the effect on weekly earnings, related more to actual labor productivity, which is also influenced by the number of days worked per week.

In our earlier study schistosomiasis in males showed a sizable and significant negative effect on potential labor productivity, as measured by earnings per day worked. The estimated effect of schistosomiasis was to reduce daily earnings of male plantation workers by some 30%. Three years later, however, and contrary to the hypothesis that the severity of schistosomiasis was increasing, we find that the magnitude of the estimated negative effect of schistosomiasis for males has (a) decreased, not increased, in magnitude, and (b) become statistically insignificant.

With regard to the effect of schistosomiasis infection on productivity per day worked on «task» jobs, our estimate for males, although not significant, has become substantially more negative than it was previously. This is consistent with the hypothesis of increasing severity of infection.

If the severity of schistosomiasis infection was increasing, we would also expect to find a more-negative effect of infection on days worked per week for the later period. And the negative effect on work-days of schistosomiasis infection among males has increased, which is consistent with the hypothesis that severity of infection was increasing. Whereas schistosomiasis infection was associated in the original study with an increase in work days, the estimate from the follow-up study is that it decreased days worked by three-tenths of a day per week, although this estimate was not significant statistically.

All of the results reported above must be qualified. During the three years between our original data and the follow-up study data, some of the workers ceased working for the Geest banana estate. Our analysis, therefore, was limited initially to

workers who were with Geest at the time of both studies, in 1968 and 1971. We now pose the question of what bias, if any, is introduced into our estimates by virtue of the worker attrition.

If, for example, the workers who left were more seriously debilitated by schistosomiasis infection — perhaps to the point of having to cease working altogether or even dying — then the effect of their omission in our follow-up would be to bias upward the true effects of schistosomiasis on labor supply and productivity. By contrast, if the workers who did not remain with Geest were the healthiest, most ambitious workers, who left to take better-paying jobs such as those in the construction industry that was booming in St. Lucia during the 1968-71 period, then the effect of their omission in the follow-up study would be to bias downward the effects of schistosomiasis. That is, the earnings and productivity of non-infected workers as a whole would be greater than the productivity of those non-infected workers who remained with Geest.

It was not possible to determine what happened to the productivity or earnings of workers who dropped out of our sample. We do know, however, some of the characteristics of the «leavers» and the «stayers» who, together constitute our original sample. Leavers, both male and female, were younger than the stayers, and proportionately fewer of the leavers had an enlarged liver or spleen, both of which are symptoms of a variety of illnesses including an advanced case of schistosomiasis.

In order to approximate the direction and magnitude of bias caused by the

omission of the leavers, we tried several alternative bases for estimating their earnings subsequent to leaving Geest plantation employment. We made various assumptions as to which of the leavers left because of illness and which left to take a better-paying job. Our preferred set of assumptions was that the «leavers» were a non-random sample from the original group, and had the following characteristics. Leavers who were young (under 30) and not infected with schistosomiasis were assumed to have left for better-paying work, while leavers who were older (45 and over) and infected were assumed to have left because of physical debility attributable to the worsening effects of parasitic infection.

Using this set of assumptions, we conclude that schistosomiasis did exert a significant negative effect on productive potential, reducing earnings per day by approximately 15%. In our earlier study, however, we estimated that schistosomiasis exerted an even larger effect, about 30%, on the daily earnings of male workers. Thus, our adjustment of the follow-up data to account for attrition did disclose a continuation of negative effects of some parasites, but it did not provide evidence in support of the hypothesis that schistosomiasis infection was exerting an increasing effect on earnings.

We should point out, however, that no world-wide conclusion can be drawn safely from any results for a single geographic area. Whether the effects of schistosomiasis infection are or are not intensifying in St. Lucia cannot tell us what is happening in other areas. Further research is needed, particularly in areas of suspected greater intensity of schistosomiasis infection.

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**THE RECENT HISTORY OF PARASITIC DISEASES IN CHINA :
THE CASE OF SCHISTOSOMIASIS,
SOME PUBLIC HEALTH AND ECONOMIC ASPECTS**

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Reopening of contacts between the West and the People's Republic of China has generated enormous interest among Western scholars in the vastness and complexity of the social experiment underway in China. Chinese medicine, particularly the apparent success of acupuncture, and the level and quality of health services generally have greatly interested the West because of our own present difficulties with the cost and quality of health services. On another front, experience in China in large public health projects is also of supreme interest to the West and to Third World countries as well. Much of the Third World is plagued with ravaging diseases, especially parasitic diseases, and the progress in China in controlling and eradicating such diseases is, therefore, of great interest to all underdeveloped nations. In 1958, it was reported that in nine years the People's Republic of China had made «unprecedented achievements in the eradication of the five major parasites [schistosomiasis, malaria, kala-azar, filariasis, and hookworm]...⁽¹⁾». There was widespread belief in Western medical circles that the pro-

gress of the first nine years was sustained and that during the 1960's China had effectively brought under control the public health aspects of these major parasitic diseases^{(2)*}.

A recent survey of control efforts, though finding much to commend in the efforts of the Chinese, was nonetheless uncertain as to the present status of the disease^(3,4). Reports on Chinese health conditions from returning visitors to China also fail to mention schistosomiasis as having been eradicated or, indeed, being in a manageable control phase^(5,6). It may well be that the ultimate goal of total eradication has sensibly been revised in favor of effective control of the rate of prevalence of the disease in already infected provinces. Whatever the actual case may be, it does not seem unlikely that schistosomiasis is still in 1975, a serious public health problem in China, much as it is in many other parts of the Third World.

Schistosomiasis has become, in the eyes of most public health experts, the most important disease in the world, rival-

* Chen (2) reports that cholera, plague and smallpox also were eradicated. He also reports the incidence rate from malaria to be less than 3%, filariasis to have been practically eradicated from 38 districts and municipalities with 2.6 million patients cured, and that the number of kala-azar patients dropped from 350,000 to 10,000 within the last 10 years. He notes that hookworm infection, however, was still widespread but that up to 4 million persons (out of a total estimated infected population of 10 million) were cured of schistosomiasis and that many areas were now entirely free of the disease.

ing only malaria, in terms of its potential for disrupting the daily lives of the people and affecting adversely the economy of a country. Estimates of the world's population infected with one or more of the types of schistosomiasis range from 120-200 million persons. Populations at risk of infection, however, may be as much as 350-400 million persons, roughly 10-15% of the total world population⁽⁷⁾. The population infected and those at high risk of infection are located overwhelmingly in the poor parts of the world in Asia, Africa, the Middle East, and Latin America.

The economic losses due to schistosomiasis have been alleged to be staggeringly high. These losses are attributed to reduced worker productivity, the reduced performance of school children, output and family income losses in communities, and to a lesser degree, mortality costs for premature deaths of young children and adults⁽⁸⁾. Few economists, however, have attempted to deal with these economic impacts and the results of those who have, to date at least, suggest that the economic impact of schistosomiasis may either be overemphasized by public health researchers, or that it is taking forms which have thus far eluded the technical skills of the economist.*

There is no reason to doubt that accomplishments in controlling the disease between 1949 and 1958 were real. Reports in Chinese medical journals indicate that a great deal of research was underway on the disease, that extensive efforts were made to kill snails by filling ditches and canals, that public health efforts in rural areas were greatly stepped up, all of which suggest that progress in controlling, if

not eradicating the disease, was considered a fundamental social goal. Some sort of milestone may have been reached in 1958⁽⁹⁾.

What makes the Chinese case so interesting, however, is the integration of social theory and policy in the fight against disease. To transform a nation wracked with disease of all sorts into a healthy, viable population is an accomplishment that requires more than factor inputs (doctors, hospitals, medicine, etc.). In the case of parasitic diseases especially schistosomiasis, the medical inputs may be much less important than the change in values and attitudes toward work, living style, and social habits. Schistosomiasis is interrelated with a particular pattern of life among a rural population and short of an effective and cheap drug, the only way to keep the disease under control requires drastic changes in the values and habits of the people.

It is certainly easy to accept the notion that during the 1950's, in the flush of victory, and with the enormous energy and effort expended in all ways in China, there were great successes in the treatment and control of schistosomiasis. This view seems to have been accepted in the West and there is little reason to doubt its validity⁽²⁾.

Did the Prevalence Rate of Schistosomiasis increase after 1958 ?

Our story is that from a high water mark reached in 1958 the prevalence rate probably did increase but we can only suggest this was so on the basis of limited and inferential evidence. In 1966 there is a call for another national conference on the disease, the first called since 1958,

* This work has been assessed by Gaylord Cummins in a paper delivered February, 1972, at a Tulane University Symposium on the «Future of Schistosomiasis Control» entitled «Economic Implications of Schistosomiasis».

and there are fewer reports of districts and villages being «cleared» of snails. In 1970 still another national conference is called^{(10,11,12)*}. Ideological training and instruction in Chairman Mao's views on the need to eradicate schistosomiasis, and how to do it, appears to have been intensified in the late 1960's, perhaps as a result of the Cultural Revolution. «Thirty thousand barefoot doctors», as one report put it, were each paying heed to Chairman Mao's teaching of «get mobilized, pay attention to hygiene, reduce disease, improve health conditions...». As this report went on further.

«Elimination of schistosomiasis is a 'protracted war,' which requires a special force armed with Mao Tse-Tung's thought and having revolutionary spirit of a high degree. At present, a special force of mass schistosomiasis prevention with poor and lower-middle peasants and their children as the mainstay who are not detached from production has been set up in the outskirts of Shanghai. According to incomplete statistics, in nine hsien, there are more than 30,000 'schistosomiasis prevention' workers, night-soil caretakers and 'bare-footed doctors.' They get together with the broad masses to play the role of the backbone in the movements for schistosomiasis prevention (13)».

Perhaps one is misled in treating this kind of indirect evidence as indicative of anything being amiss. But the urgency with which the rhetoric of the schistosomiasis problem is presented in the previous quotation and the appearance in the international press of the information that a major schistosomiasis problem still existed in China, while not conclusive evidence, does suggest a picture much different than was portrayed in the West a decade earlier.

The burden of our claim, however, that the prevalence rate increased, or at least was not substantially reduced, during the 1960's rests on an inferred link between irrigation and water conservancy construction and the spread of the disease. Schistosomiasis is a water contact disease: the propagation of the life cycle of the carrier snail and the human or animal host is intimately connected to water contacts. Water conservancy projects, irrigation and power-dam construction may have done as much in the past decade to spread schistosomiasis infection as any other human action. The Aswan Dam, power dams in Africa, and irrigation construction in Brazil, the Philippines and elsewhere in the Third World countries all have been implicated in the growing proportions of populations infected with schistosomiasis or at greater risk of infection^(14,15).

During the Great Leap Forward in China (roughly 1958-1964), an important emphasis was placed on water conservancy, power dams, and irrigation construction. Quantitative evidence on the magnitude of these efforts is hard to come by. But an important part of the story has been carefully reconstructed by Kang Chao⁽¹⁶⁾. The limited quantitative information does suggest that irrigation construction and water conservancy projects grew during the first years of the Great Leap Forward especially in the 12 schistosomiasis provinces where greater proportions relative to the nation of their cultivated acres were under irrigation.**

* On the tenth anniversary of the publication of Chairman Mao's poems, «Farewell to the God of Plagues», the district for which the poem celebrated the victory over schistosomiasis, Yukiang County in Kiangsi Province, reported the great progress made since 1958, but nowhere in the report did it claim the county was free of schistosomiasis infection. In 1969 a number of reports appeared concerning efforts made in Shanghai and the success achieved. Elimination of the disease was not claimed⁽¹³⁾.

** It should be noted that irrigation increased in Northern China as well, and at rates comparable to those in Southern provinces. There, however, the actual area irrigated was a smaller proportion of total crop land than in the south and the irrigation method used was redirecting underground water flow through well drilling.

These points are illustrated in Tables 1 and 2.

TABLE 1. — Irrigated areas (10,000 Mou) in China

Province	1957	1958	(Rate of Increase)	1959
Kiangsu	3,830	5,491	(43.4)	4,390
Honan	4,300	10,000	(132.6)	—
Anhwei	3,400	5,500	(61.8)	6,100
Chekiang	2,500	2,670	(6.8)	—
Hupei	2,800	2,970	(6.1)	—
Kiangsi	2,900	3,440	(18.6)	3,522
Fukien	1,480	1,804	(21.9)	—
Hunan	—	—	—	—
Kwangtung	2,090	3,590	(71.8)	4,400
Kweichow	793	1,690	(113.1)	—
Yunnan	1,230	1,500	(22.0)	2,238
Kwangsi Chuang	2,496	3,696	(48.1)	2,478
Shanghai Municipality	—	—	—	—

Sources: Social Science Research Council, *Provincial Agricultural Statistics for Communist China*, (Cambridge, Massachusetts, 1969). Compiled from various provincial tables.

TABLE 2. — Irrigated areas in China as a percentage of total cultivated area, 1958
(10,000 Mou)

Province	Cultivated Area	Irrigated Area	Ratio
Kiangsu	8,304	5,491	66.1%
Honan	13,600	10,000	73.5%
Anhwei	8,733	5,500	63.0%
Chekiang	3,140	2,670	85.0%
Hupei	6,800	2,970	43.7%
Kiangsi	—	3,440	—
Fukien	2,219	1,804	81.3%
Hunan	5,313	—	—
Kwangtung	5,800	3,590	61.9%
Kweichow	3,136	1,690	53.9%
Yunnan	4,110	1,500	36.5%
Kwangsi Chuang	3,846	3,696	96.1%
Whole Nation	161,680	107,000	66.2%

Sources: Social Science Research Council, *Provincial Agricultural Statistics for Communist China*, Compiled from various provincial tables.

Kang Chao, in his recent work on **Agricultural Production in Communist China**⁽¹⁶⁾ has suggested two additional factors concerning the construction of irrigation facilities which could support the view we are suggesting. Chao has noted a change in the pattern of irrigation during the 1959-1962 period. Prior to this the water pond which combined both the gravity and water-lift methods were most commonly used as irrigation facilities in the rice regions. Water was lifted from ponds into relatively short distribution channels where gravity then carried the water to the adjoining rice field. The ponds also were receptacles for surface run-off water and drainage from the rice paddies. Each pond, therefore, was in a sense a geographically localized irrigation system. To a large extent this would tend to keep schistosomiasis infections localized to the extent of the distribution of populations around these pond-centered irrigation systems. New irrigation construction in the 1958-59 period, however, carried well beyond these localized ponds and was on a much larger scope, and via gravity principles, permitted larger areas of rice land to be irrigated. Distribution channels became larger and were now inter-connected to form an irrigation network making this input available on a much more expanded geographical scope than was previously the case. The potential for spreading schistosomiasis infection to previously «disease free» parts of the population would appear to have been enhanced as a result of these developments in irrigation practice and construction.

A second point Chao suggests has to do with the change in the cropping system which occurred simultaneously with the expansion in irrigation networks in the rice regions. Previously, a large part of the rice region grew two different

crops a year. Rice was grown with rain water which had been stored in ponds and other receptacles during the rainy season. After the rice crop was harvested a different winter dry-land crop was planted. With the availability of year-round water supplies as a result of irrigation construction, farmers in the rice regions shifted to two continuous crops of paddy rice. This change in the cropping system suddenly increased problems of pest control. The previous two alternate crop systems, it appeared, had some ecological balance to it by not permitting sufficient breeding time for pests for either crop to become a major problem. There have been reports, Chao notes, that continuous cropping systems create a more favorable environment for the breeding of *Pyralididae*, i.e. moths which attack the rice plant. It is not too farfetched to speculate that the continuous cropping of paddy rice fields also has permitted the snails to survive and reproduce over longer time periods than had been true in pre-1958 China⁽¹⁶⁾. It also has provided the opportunity for a longer work year and by so doing probably increased the risk of infection for agricultural workers.

The Economic Impact of Schistosomiasis

The final part of our story is whether or not it matters in any relevant economic-demographic sense, if, indeed, the prevalence rate for schistosomiasis increased during the 1960's. There is little doubt that, in the minds of party leaders, and especially in that of Chairman Mao, schistosomiasis did have a profound demographic and economic impact in China. Statements in the 1950's and the renewed attack on schistosomiasis in the 1960's and at present, all suggest that the cost of the disease is not simply the human suffering involved but also a loss in the productivity of workers, the lessen-

ed fertility of women, and the diminished alertness and attentiveness of school children. That is, just as western economists have come to treat expenditures on health as both consumption and investment (in augmenting the quantity and quality of human capital) so has Chairman Mao. But, of course, the Maoist view goes well beyond the western concept of «human capital». As recently as August, 1969, the relationship between schistosomiasis and agricultural production, for example, was explicitly noted⁽¹³⁾. In one provincial report after another for earlier years, especially in the 1950's, a linkage between the health of workers and their productivity in agriculture and «party» duties as well as the effects of schistosomiasis on the fertility of women and the performance of school children was well recognized. One statement which seems typical of the perceived relationship between health and productivity is as follows :

«Health work must proceed with a view to developing production; it should be closely integrated with and serve production. Under the unified leadership of the party committees, production and health work must be closely coordinated and planned. The more intense the production, the more attention must we pay to health work; the better the health work is done, the higher will be the production level. This, in a nutshell, is the dialectic unity in the relationship between production and health (18)».

One report, in 1960, stated that «on the average, the disease causes a 40% loss in the patients' capacity to work...⁽¹⁹⁾» No doubt the Chinese literature, sparse though it is, also reports purported economic benefits from schistosomiasis control, treatment and eradication. Four farming cooperatives in Hunan province, for example, reported a gain in total population between 1955 and 1957 of about 15%, an increase in rice production of 10.8% and a gain in the total work points of from 19% to 44% over the same

years, after schistosomiasis was believed to have been eradicated⁽¹⁾. In Rentun Village in Shanghai a population increase between 1949-58 of 31.3% was attributed to schistosomiasis control, as was a doubling of the labor force and a threefold increase in average yield per man of rice land⁽²⁰⁾. Over the same period a report from Jiashan County, Chekiang Province also reported a threefold increase in the labor force and a rise in individual income of brigade members of 1.5 times. «Women for years childless», this report also noted, «are now proud mothers⁽¹¹⁾».

One does not know what to make of these reports. In view of work done on schistosomiasis and its presumed economic effects elsewhere, it is not too likely that these reported demographic and economic effects can be attributable to schistosomiasis alone. As Jordan and Webbe⁽¹⁷⁾ have commented : «Convincing evidence that schistosomiasis is invariably a serious public health problem is lacking, and the importance attached to it will vary from place to place in relation to other diseases and the socio-economic conditions prevailing⁽¹⁷⁾». Only a few studies have attempted to isolate the demographic and economic impact of health variables or specific diseases.

It is therefore difficult to evaluate reported morbidity rates such as that of 40% quoted above, or these reported for 10 villages in Kiangsu Province and for the Tianning People's Commune in Chekiang Province. In Kiangsu Province a morbidity rate of 35-40% was reported for the period 1945-55 and a rate of 26.67% in 1957. In the Tianning People's Commune in the early years of the anti-schistosomiasis campaign in that area (Jiashan County), it was noted that 76% of those in the late stage of the disease «were unable to work»^(8,21,22).

Nonetheless, there are perhaps good reasons for thinking that schistosomiasis could have substantial demographic and economic effects in China.

1. Schistosomiasis in China also affects animals, particularly work animals. It was reported in 1959 that 2.5 million oxen were infected with schistosomiasis. What proportion of the total oxen population this figure represents is not known (23, p. 496). Studies in the Philippines show that certain domestic animals were capable of transmitting the cycle of infection even if human transmissions were controlled. Dogs and cows were both found to be most effective in transmitting large numbers of eggs in their faeces. High prevalence rates were also found in cats, water buffalo, pigs, horses, sheep and goats, wild mice and rats⁽¹⁷⁾. Two work animals, oxen and water buffalo, proved highly susceptible to schistosomiasis infection. A survey made in August, 1957, for 10 hsien of Kiangsu Province, where 11,000 water buffalo and oxen were examined, revealed infection rates of 10.73% and 40.13% respectively. This same study also reported on the correlation of human and animal infection rates in Kiangsu and Hunan provinces. Animal and human infection rates were nearly identical in all the cases examined^(24,25). This suggests a strong linkage between place of work (in the paddies) and infection for both humans and animals.

The potential impact of animal infection on humans might go in the following direction: (a) continued transmission of the disease cycle, the chances for human reinfection being greater than when humans are the only hosts; (b) high prevalence and infection rates of animals could seriously deteriorate the nutritional value of the populations' food supply in case the animals are used for food; (c)

morbidity of animals used in agricultural production, particularly of the water buffalo, would reduce the efficiency of capital used by farmers and could potentially lower per man acre yields.

2. The severity of *S. japonicum* infections, the type of schistosomiasis found in China, appears to be high as compared with other types of schistosomiasis. We have no comparative studies of demographic or productivity effects from the different types of schistosomiasis. But piecing together studies on *S. japonicum* and *S. mansoni* suggests that *S. japonicum* is more likely to produce serious physiological complications than *S. mansoni* and that the probability of higher intensity of infection (at comparable egg counts) for *S. japonicum* is more likely^(17,26,27). All of this suggests that the likelihood exists that *S. japonicum* will have greater economic impact than studies in the West, largely on *S. mansoni*, would suggest.

Of course these are just conjectures: the data simply are not available to perform any kind of a reasonable test which could isolate the demographic and economic effects of schistosomiasis from the many other factors that affect population, output, and productivity changes. A few pieces of potentially useful information are available and we shall attempt to see what these data might indicate in the way of a positive relationship between schistosomiasis and important demographic-economic effects. It should be emphasized, however, that the most important piece of information which would be necessary to causally link schistosomiasis and economic-demographic factors is the intensity of infection of the population. That is to say we do not know, quantitatively, how «sick» the people are and whether or not being «sick» in some

clinical-physiological sense will affect their performance at work, non-work, etc. At present there is no way to infer intensity of infection from experience elsewhere. Thus, the evidence we present below presumes that a population with schistosomiasis will have its performance, its behavior, affected. If we are not able to capture any aggregate effects, it does not mean that population growth or labor productivity was unaffected by schistosomiasis. Rather it means we cannot capture it from the data and model specification employed. And even if a positive association is «proved» not to exist between schistosomiasis and economic-development variable, it does not really mean that the population's behavior and performance in non-work, non-reproduction capacities is not affected.

What we propose to do is look first at some possible demographic effects in the 12 major schistosomiasis provinces.

We shall then look at the possibility that schistosomiasis had output and labor productivity effects in the rural-agricultural sector of these provinces.

Demographic Effects

In Table 3 we show the population of schistosomiasis infected regions, and in Table 4 the percentage changes in the growth of population for 12 provinces. If schistosomiasis had been successfully eradicated or brought under control in the 1950's, a strong hypothesis would predict that rates of growth (ignoring lags) in these disease infected areas would exceed growth elsewhere, all other things being equal. As shown in the table, five provinces grew less than the nation did and seven grew more. The highest growth change occurred in Kweichow and Fukien. Fukien is a coastal province along the Taiwan Strait and the population increase

TABLE 3. — Population of schistosomiasis infected provinces in China, 1953-1964
(in 1000 persons)

Province	(June 30) 1953	1957	1964
Kiangsu	41,252	54,230	47,000
Honan	44,215	48,670	50,000
Anhui	30,633	33,560	35,000
Chekiang	22,866	25,280	31,000
Hupei	27,790	30,790	32,000
Kiangsi	16,773	18,610	22,000
Fukien	13,143	14,650	17,000
Hunan	33,227	36,220	38,000
Kwangtung	36,740	37,960	42,000
Kweichow	15,037	16,890	17,000
Yunnan	17,473	19,100	23,000
Kwangsi Chuang	17,591	19,390	24,000
Shanghai Municipality	—	—	—
Total Infected Areas	316,740	346,350	378,000
Population, Whole Nation*	587,960	646,530	713,400
Infected Areas as % of Whole Nation*	53.9%	53.6%	53.0%

* These figures exclude Taiwan and overseas Chinese, and are for year end.

Sources of data: a. 1957-1964: *China Monthly*, Hong Kong, No. 56, November 1, 1968, p. 15.

b. 1953-1957: N.R. Chen, *Chinese Economic Statistics*, (Aldine, Chicago, 1967), p. 124.

c. Also letter to Ralph L. Andreano from John Aird, dated June 22, 1971.

TABLE 4. — Growth of population in schistosomiasis infected provinces, in China, 1953-64

Province	Percentage Change	
	1953 to 1957	1957 to 1964
Kiangsu	9.6%	3.9%
Honan	10.0%	2.7%
Anhwei	9.6%	4.3%
Chekiang	10.6%	22.6%
Hupei	10.8%	3.9%
Kiangsi	10.0%	18.2%
Fukien	11.5%	16.0%
Hunan	9.0%	4.9%
Kwangtung	3.3%	10.6%
Kweichow	12.3%	0.7%
Yunnan	9.3%	20.4%
Kwangsi Chuang	10.2%	23.8%
Shanghai Municipality	—	—
Population*, Whole Nation	10.0%	10.3%

* These figures exclude Taiwan and students outside of China.

Source : Table 3.

could well be associated with an increase in the armed forces. Also, between 1953 and 1957 demarcation lines of individual provinces were changed and perhaps these changes account for population changes rather than real rates of natural increase. And of course, national population policy effects may also be intertwined with these observed population changes.

In the 1957 and 1964 period, when (again ignoring lags) we suggest the prevalence rate increased, a strong hypothesis would predict that the population growth of the schistosomiasis provinces, all other things being equal, would be significantly less than in non-schistosomiasis provinces.

For the period 1957-64, six of the provinces have higher rates of growth than the country as a whole (though this

depends somewhat on the whole nation population figure used). These provinces were : Chekiang, Kiangsi, Fukien, Yunnan, Kwangsi Chuang, and Kwangtung. Yunnan and Kwangsi Chuang are both border provinces and their growth changes during this period might be the result of a deliberate population relocation policy or comparatively rapid industrialization. Fukien's population changes are probably again associated with military build-up, but the cases of Chekiang, Kwangtung and Kiangsi are quite interesting for our purposes. If, in fact, higher infection and prevalence rates followed higher rates of irrigation construction, one should expect, if schistosomiasis had any demographic effects, lower rates of growth in higher irrigation areas than in lower irrigation ones. Referring back to our earlier table on irrigation construction, both Chekiang and Kiangsu had less

than average amounts of water conservancy and irrigation construction during the Great Leap Forward. This may have been due to the topographical factors in both provinces, but it is just possible that because of lower irrigation construction these two provinces may have escaped any gains in increased infections in the early 1960's and continued to enjoy some relative equilibrium in schistosomiasis eradication and treatment work, with a concomitantly large population result.

Output and Labor Productivity Effects

We have assembled a limited amount of information to see whether or not any light can be shed on the possible link between an increase in the prevalence rate of schistosomiasis after 1958 and the output of agriculture and the productivity of workers in the schistosomiasis provinces.

Relative Yield of Rice Land. If schistosomiasis had large positive output and productivity effects in agriculture, we

would postulate that rice yields — the principal crop of the 12 provinces — relative to other crops, all other things being equal, should decline. Similarly, if schistosomiasis prevalence was reduced and there existed positive productivity effects, we should expect relative yields of rice lands to increase. Table 5 gives little evidence to support our expectations, i.e. that between 1952 and 1957 the relative yields rose and that between 1957 and 1965 they fell. In fact, as shown in the table, the unit yield of rice land relative to land under all food grains rose only slightly from 1952 to 1957, and from 1957 to 1965, instead of falling it rose by 7.3 percentage points. Stability in the relative yield of rice land is perhaps the most plausible interpretation one could give on the data in Table 5. Any labor productivity effects (positive or negative) that may have existed could have been offset by a large and complex number of other factors (such as climate, fertilizer inputs, etc.) that determine the yield of rice.

TABLE 5. — Comparative yield of rice land in China, 1952-1971 (a)

Year	Crop acreage (in 1,000 mou)			Output (in 1,000 short tons)			Unit yield
	Rice	All food grains	Rice as % of all food grains	Rice	All food grains	Rice as % of all food grains	Rice land relative to land under other food grains (Percentage points)
1952	425,734	1,684,491	25.3	68,450	154,400	44.3	175.1
1957	483,617	1,813,273	26.7	86,800	185,500	46.8	175.3
1965	—	—	23.0	101,412 (b)	—	42.0	182.6
1970	—	—	—	—	240	—	—
1971	—	—	—	—	246	—	—

(a) Sources, For 1952 and 1957 data, N.R. Chen, *Chinese Economic Statistics*, pp. 287 and 338. Aldine Publishing Company, Chicago, 1967; for 1965 data, *People's Daily*, February 7, 1966; for 1970 and 1971 data, Durdin, T. China discloses figures on grain output, *New York Times*, p. 12, April 2, 1972.

(b) Rice output figure for 1966, from an estimate by the Food and Agriculture Organization of the United Nations, cited in U.S. Bureau of the Census, *Statistical Abstract of the United States*, p. 818. Government Printing Office, Washington, D.C., 1970.

Output Per Worker. Data on estimated average output per worker for the 12 schistosomiasis provinces between 1954-1957 also suggest that if schistosomiasis control was producing positive effects on labor productivity, it is not discernible from a whole array of other competing and offsetting effects. We show in Table 6 the output per worker for all food grains for the 12 provinces. If these data are to be believed, they show a marked fall in average output per worker for every province except Kweichow, as well as for the

whole country. The appropriate prediction, if schistosomiasis had large productivity effects, would be or either a rise or no change, in average output per worker. On the other hand, if schistosomiasis did have large negative labor productivity effects (the magnitude of these effects would, of course, become benefits, all other things being equal, if the disease were eradicated) the appropriate prediction is for a fall both in the average and marginal product of labor.

TABLE 6. — Output of food grains per worker in 12 Schistosomiasis infected provinces in China, 1954-57.
(Catties)*

Province	1954	1957
Anhui	3,000	2,000
Chekiang	3,000	1,000
Fukien	3,000	1,000
Hunan	3,000	1,000
Kiangsi	4,000	2,000
Honan	4,000	1,000
Hupei	4,000	2,000
Kiangsu	3,000	1,000
Kwansi Chuang	4,000	1,000
Kwangtung	4,000	1,000
Kweichow	1,000	4,000
Yunnan	4,000	1,000
Whole Country	3,000 (1,500)	1,000 (1,200)

* a catty = 1.1 pounds.

Source : Total output of food grains from Chao, *Agricultural Production in Communist China*, p. 304, Appendix Table 14.

Agricultural labor force estimate by province by applying estimate of proportion of agricultural labor to whole population to each province from data in Chen, *Chinese Economic Statistics*, p. 474, Table 11.2.

The bracketed whole country figures refer to output estimates by Chao for 1954 divided by a 1952 total agricultural labor force estimate of Chen and for 1957 a 1957 Chao output estimate divided by a 1958 Chao labor force estimate.

The point is, therefore, for an economy such as China had during the 1950's, total output could be maintained because of the large elasticity of supply for labor but at the same time disease effects on average and marginal products could still occur. If we reject the notion that substantial improvements — in the sense that positive benefits were produced — occurred in treatment and control of schistosomiasis during the 1950's, the story in Table 6 — a fall in average product per worker — is consistent with there being disease effects on labor productivity and with a growth in total output of food grains. However, during the 1950's, grain output fell and the inputs of labor rose and did so much faster than all other agricultural inputs (fertilizer, tractors, draft animals, etc.). To be sure, natural disasters, weather, etc., are important explanatory considerations. But perhaps disease effects on labor productivity were indeed strong and the measure of success achieved in controlling schistosomiasis during the 1950's was overestimated.

Population-Irrigation-Rice Yield Effects. The limited evidence discussed thus far is not strong enough to support the two basic disease hypotheses under discussion: (1) Between 1953 and 1958 the prevalence rate of schistosomiasis declined, and (2) after 1958 the prevalence rate rose. The demographic-economic impacts occur inversely for each hypothesis. But as we have already discussed for both demographic, labor productivity and output impacts we have at least two effects to consider: (1) productivity and output gains from improved irrigation, and (2) a rise in the birth rate because productivity and output gains increase family income. Working against these two effects are the disease effects: if schistosomiasis is eradicated (assuming this does have positive productivity and output effects) this,

too, could increase labor productivity, rice yields, and output per man. Similarly, if schistosomiasis is eliminated, (and it does have positive effects on birth rates) an increase in population through changes in birth rates would occur. Conversely, if schistosomiasis prevalence increases, the effects would work in the opposite, i.e., negative, directions. What we cannot know, from the limited data available, therefore, is the separate impact of these potentially offsetting effects, or whether or not disease effects are swamping non-disease effects on labor productivity, output and population changes in the schistosomiasis provinces.

We decided, because of this difficult identification dilemma, to pool all the information we had for the 1953-58 period, and to see if a test of the hypothesis — that the prevalence rate for schistosomiasis improved or declined during this period — could be put to somewhat more rigorous form.

The evidence we are going to pool is the change in population growth (x) between 1953 and 1958, the proportion of cultivable land under irrigation in 1958 (y), the rate of growth of new irrigation construction 1957-58 (z), the average yield of rice in 1958 for each province (w), and the percentage of the sown area in each province in rice production (s). What we do with these pooled data is to put the relative changes in ranked form for each province and compute Spearman coefficients of rank correlation. The average output per worker data are not included in the pooled information because these data are based on our own estimates and there is not enough variation to warrant a precise ranking.

If we accept the hypothesis of improvement between 1953/4-1957/8 in schis-

tosomiasis infection, we should expect positive signs and high values for r_{xy} between xy , xz , xw , wz . That is, there should be a high positive correlation between rank in irrigated land and change in population for each province (xy). Similarly, rice yield rank (w) and irrigation rank (y) would be negatively correlated if the impact of schistosomiasis on productivity swamps the effect of irrigation on productivity, or positively correlated if the reverse were true. The computed rank correlation coefficients are as follows:

- | | |
|----------------------|----------------------|
| (1) $r_{xy} = -0.03$ | (5) $r_{wy} = 0.13$ |
| (2) $r_{xz} = -0.31$ | (6) $r_{xz} = -0.41$ |
| (3) $r_{xw} = 0.30$ | (7) $r_{ws} = 0.52$ |
| (4) $r_{wz} = -0.43$ | |

With the exception of r_{xw} , which is not strong enough to support the hypothesis, the coefficients (r_{xy} , r_{xz} , r_{wz} , and r_{xs}) in sign and magnitude require a rejection of the hypothesis of improvement. Moreover, the finding that $r_{xz} < r_{xy}$ may suggest that the negative effects of schistosomiasis on population growth after 1958 could be swamping all other effects; for it is beyond 1958 that the big push in water conservancy, power dams, and irrigation construction occurred on a much larger scale than was true between 1954 and 1957. Similarly, the high and negative coefficient of rice yield (w) against the rate of change in irrigation (z) suggests that negative disease effects may also have been dominating positive productivity effects from new irrigation. Though positive, the low value of r_{wy} — average yield on rice land against the proportion of cultivable land under irrigation — may suggest that the output effects of irrigation were being constrained by disease effects. Indeed, $r_{ws} > r_{wy}$ seems to also support this explanation and to provide strong support to the idea

that total output could be maintained, even if disease productivity effects were large, by adding more labor to existing land under rice cultivation. The interpretation of r_{ws} is that yields (per man, per unit of land) are high and positively correlated with the amount of sown area in each province under rice production.

While admittedly this evidence is hardly conclusive, it does suggest that between 1953/54 and 1957/58 the probable degree of improvement in schistosomiasis infection was less than was supposed. For the post 1958 period we are given to conjecture. For example if r_{wz} continued to hold — i.e., that average rice yields were negatively correlated with the rate of increase in irrigation construction — and r_{ws} remained positive, one might be observing for the post 1958 period the maintenance of total rice output but with larger labor/land combinations required because of negative labor productivity effects due to an increase in the prevalence rate of schistosomiasis. While one doesn't wish to push this line of reasoning too far, if the relationship that appeared to exist during the 1950's between the demographic-economic variables and disease effects continued to dominate Chinese experience in the 1960's, there would seem to be cause for concern — as apparently there has been and continued to be — with the economy wide effects — as well as the individual human suffering effects — of the spread of schistosomiasis infection.

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THE ECONOMIC DIMENSION OF SCHISTOSOMIASIS : AN ECONOMIST'S PERSPECTIVE

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Concern with the economic dimension of schistosomiasis has a specific purpose : to determine the nature and size of the economic benefits from control of the disease.

Why should this be considered desirable ? No country has, or is ever likely to have, sufficient resources at its command to satisfy all of its objectives in their entirety. This, in a nutshell, is the economic problem. The severe scarcity of resources in developing countries in particular poses the need for rational choice among the multitude of competing claims, and hence the need for establishing priorities among programs in such a way as to ensure that resources are allocated only to those programs whose net contribution to developmental objectives is greatest. In principle, both the benefits and the costs of programs within the health sector need to be enumerated and evaluated in order to achieve an optimal allocation of scarce developmental resources both within the health sector, and between the health sector and other sectors of the economy. There is nothing which exempts the health sector from enquiry into whether the benefits of its activities warrant the cost of the resources vested in them ; like all activities, health sector programs yield benefits and incur costs, the profile of which determines their relative social value. The health sector must compete with other

sectors of the economy to attract resources to fund its programs and must be able, in principle at least, to justify its claims by demonstrating that the benefits of its programs outweigh the opportunity cost of releasing resources for their implementation, from both within the health sector and from other sectors of the economy.

It is this context of sensible resource allocation which defines the need to specify the economic dimension of schistosomiasis. In practice the requisite benefit-cost evaluation may prove difficult to undertake and inexact in its conclusions — and this will certainly be true of a schistosomiasis control program — but «there is more to be said for rough estimates of the precise concept than precise estimates of economically irrelevant concepts» (Mishan, 1971). Moreover the pragmatism of self-interest favors this attitude : the need for sensible economic justifications of schistosomiasis control to secure funding has been repeatedly stressed by individuals and agencies within the public health world (WHO, 1967, 1973). It remains true that effective schistosomiasis control programs will require multi-donor support which in turn is likely to call for an acceptable benefit-cost justification in place of the vague generalisations about potential benefits which have hitherto constituted the nature of the claim.

Nevertheless, efforts to determine the economic dimension of disease continue to confront resistance from those who question the propriety of basing the decision whether to control disease on seemingly materialistic considerations such as its contribution to increased output, at the expense of 'humanitarian' considerations in terms of the suffering which it averts. This objection stems predominantly from a fear that emphasis on what is perceived to be the strictly economic benefits of disease control will dominate the resource allocation decision to such an extent that control programs which cannot demonstrate substantial economic benefits will fail to secure support, despite the humanitarian concern which they appropriately merit. While understandable, this fear clearly results from a failure to appreciate the dual nature of the economic benefits whose measurement economists consider an essential element of any assessment of the desirability of undertaking disease control programs. In general these benefits fall into two categories which reflect the fact that health is desired partly as an end in itself and partly as a means of obtaining other ends:

(1) *Consumption or independent benefits*, which accrue to the extent that disease control programs provide utility (happiness) by reducing the disutility (distress or unhappiness) associated with ill-health.

(2) *Investment or instrumental benefits*, which accrue to the extent that disease control programs favorably affect developmental objectives such as increasing the rate of growth of per capita output, improving the distribution of income, and expanding rural employment opportunities. These benefits of control programs are mediated by the effect of improved health status on many

variables, including in particular: the quantity and quality of cooperant factor inputs (labor, capital and land), the nature of their combination in production (technology), and the size and composition of the population base (the set varies with the nature of development objectives under consideration).

The fact that both independent and instrumental value is attached to certain programs (especially in the health and education sectors) and that attempts are made to estimate their instrumental value need in no way detract from their independent or consumption value. While it may appear offensive to treat human beings as in some sense analytically similar to machines, this in no way implies that they should not be regarded in other senses as quite different; indeed failure to appreciate the investment dimension of many humanitarian expenditures has in the past obviously resulted in priority in these matters being given to machines. There can be no reason for complaint where the two components of benefit (relative to the costs of implementation) together reinforce the case for disease control. Nor can there be cause for complaint where programs yield merely consumption benefits of an intangible nature whose value cannot be held to outweigh the value of the resources required to implement them. Although health for its own sake is assigned considerable value (increasingly so in developing countries) its value is not infinite, nor is its production costless. In the case of schistosomiasis the consumption benefits of control in terms of the suffering that it would avert have always been recognised to exist. Yet it is clear that these have not been perceived by governments to be large enough by themselves to warrant the considerable cost of mounting serious control efforts on a large scale. It is for this rea-

son that schistosomiasis has also engaged particular attention as a health problem believed to impose seriously adverse economic effects (in those economies where its prevalence is high), and one whose elimination would therefore generate instrumental benefits* sufficiently large, in conjunction with its consumption benefit, to warrant the cost of investing in its control. This increasing emphasis on the 'economic' dimension of schistosomiasis has produced a burgeoning literature addressed to the identification of the linkages between schistosomiasis and economic variables, and to the valuation of the economic benefits that would accrue from control. It is the purpose of this paper to evaluate these efforts in terms of the adequacy of the conceptual apparatus and assumptions which they have brought to their task, and to draw conclusions for future work from the inadequacies which critical review will expose. Although the complex problem of determining the benefit-cost profile of alternative control strategies will fall outside the scope of the present paper, it should be noted that some useful but embryonic work involving epidemiological models and computer simulation of the time profile of benefits and costs of control strategies (mollusciciding and chemotherapy) has been carried out (Jobin, 1973; Paulini, 1974), and that further research in this area should be encouraged to increase the ability to design optimal programs for schistosomiasis control.

While the question of identifying the linkages between schistosomiasis and economic variables is logically prior to that of valuing the economic outcome of

changing the prevalence of schistosomiasis through control measures, these questions have been considered in reverse order in the chronological sequence of the literature. In emphasis of the significance of this fact, the following treatment will observe the same sequence.

The Economic Dimension of Schistosomiasis

Although the general hypothesis that 'schistosomiasis causes economic effects' is freely used in discussion of the benefits of schistosomiasis control**, there seems to be little conscious recognition of the implicit structure of assumptions which underlies this claim. Because the failure to break down the hypothesis into its component elements is the source of much ambiguity, confusion and error in consideration of the linkage between schistosomiasis and economic variables, and of the gains from schistosomiasis control, it will prove worthwhile to preface the following critique with a closer examination of the general hypothesis which lies at the heart of the issues at hand.

Essentially the hypothesis proceeds as follows: that (1) schistosomiasis (defined as the state of infection with worms of the genus *Schistosoma*) implies (2) a degree of intensity of infection, or load of schistosome worms (as proxied by the size of egg output in the urine or faeces) which leads to (3) a degree of severity of resultant disease (in clinico-pathological terms) which in turn leads to (4) a degree of physical/mental dysfunction, or deviation from a condition of functional

* or strictly economic benefits, as non-economists think of them.

** For example «the infection rate of *S. mansoni* among farmers may reach up to 80% in some areas. This undoubtedly contributes significantly to the reduction in productivity of the farmers». (Omar and Ahmed, 1974).

well-being, which finally leads to (5) an economic effect in the form of some unfavorable effects on some economic variable (usually labor productivity or, alternatively, labor supply) (see Fig. 1). Thus the general hypothesis that schistosomiasis affects economic variables assumes that the mere presence of infection initiates a whole sequence of casual linkages — that each of the four implicit sequences are activated. The questionable nature of this assumption that the linkages between each of these five states do not break down at any stage is significant and should be borne in mind as the critique proceeds.

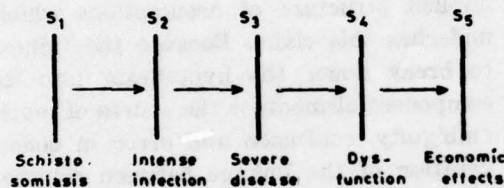


Fig. 1. The structure of the hypothesis.
 S_i defines states, $i = 1-5$.

A. Macro-Analysis

Several attempts have been made to assign a quantitative value to the economic benefits that would accrue from schistosomiasis control (Khalil, 1949 ; Wright, 1951, 1972 ; Watson, 1948 ; Farooq, 1963, 1967 ; Egyptian Ministry of Publ. Health, 1971, 1972, unpubl.). These studies, all of which assert that dramatic benefits would accrue from control, identify the debilitating consequences of schistosomal infection as the key parameter in analysis of the economic effects of schistosomiasis. The reduced form of the hypothesis is that schistosomiasis impairs the individual's capacity for sustained physical effort (imposes dysfunction) and therefore reduces the productivity of infected labor below what would otherwise be attained in a state of freedom from infec-

tion (i.e. $S_1 \rightarrow S_4 \rightarrow S_5$ in terms of Fig. 1).

In principle, determination of the size of the postulated effect requires **firstly**, the formulation of a standard of output and **secondly**, estimation of the degree to which infection causes a departure from that standard. Each investigator has approached these requirements by using some measure of the average product of labor as the labor output norm, and an assumed percentage coefficient for the so-called «loss of working capacity» (dysfunction) caused by infection as a measure of the extent to which the output of infected labor falls short of that norm. The use of this measure has in each case rested on the implicit but crucial assumption that labor's «capacity» to perform work (and this is neither measured, nor even defined) is synonymous with **actual** labor productivity at work, so that the reduction in labor productivity is **directly** proportional to the reduction in «working capacity». This assumption of linearity in the relationship between dysfunction and economic effect is denoted by the curve X_1 in Fig. 2.

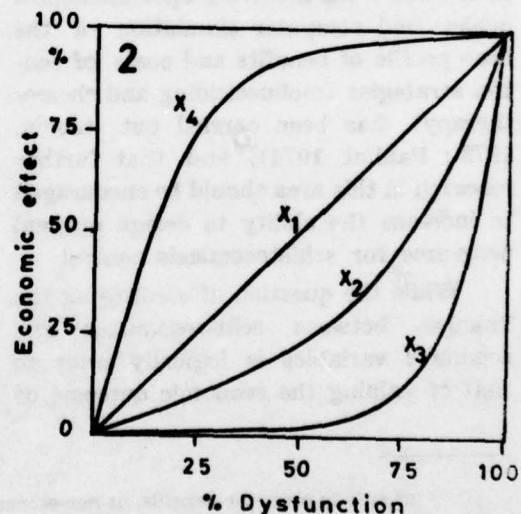


Fig. 2. Relationship between dysfunction and economic effects.

The investigators have then proceeded to multiply the output norm by the loss of working capacity coefficient to yield the loss of output per worker, with an implicit assumption of homogeneous morbidity experience among the infected population (i.e. that all infected individuals experience identical ill-health). Further multiplication of the loss of output per worker by the total number of individuals infected in the community yields an estimate of the annual 'economic loss' attributable to schistosomiasis, implicitly assuming that all infected individuals are engaged in homogeneous productive activity (i.e. that labor is equally productive in all occupational activities). Formally, the model employed to generate the 'economic loss' estimate takes the general form :

$$K = N (\alpha \bar{Q})$$

where K = annual 'economic loss'

N = number of individuals infected

\bar{Q} = annual average labor output

α = percentage 'loss of working capacity' coefficient.

To date it is models of this type which have been the only source of estimates of the gains from schistosomiasis control, and the fact that these estimates* have been adduced in favor of control renders their exposure to criticism especially important. In Egypt, for example, a 10-year eradication program has been designed on the basis that «...the economic loss to the country is £ 214,000,000 annually». (Egyptian Ministry of Publ. Health, 1971, unpubl.), calculated along the lines of the simplistic macro-model outlined above. Similarly, contemplation of a World Bank

funded schistosomiasis control program in the Philippines has produced statements such as «Being a major cause of morbidity in the rural areas, the disease, understandably, adversely affects agricultural productivity. Estimated annual loss approximates \$100 million in terms of disability, cost of treatment and death». (Philippines Dept. of Health, 1974a,b). The model rests essentially on four implicit assumptions, all of which, as will become obvious, are suspect in the extreme.

1. *Any degree of physical dysfunction necessarily entails the same degree of reduced productivity*

This assumption, although a convenient analytical simplification, poses two serious problems, the first of which concerns the definition of the two states (S_1 and S_2) between which a linkage is assumed, the second of which concerns the nature of this assumed relationship. On the first problem, the definition of the economic effect (S_2) is clear: simply a reduction in the productivity of labor. But the definition of the state (S_1) which generates it is not: how can dysfunction be defined and quantitatively expressed so that it can be employed to explain the variance of some dependent economic variable? It seems remarkable that none of the very substantial «loss of working capacity» coefficients assumed in the macro-studies have been sustained by any empirical foundation whatsoever, and that almost no empirical research has been undertaken into this crucial linkage between schistosomal infection and some indicator of dysfunction (the sequence $S_1 \rightarrow S_2$). The only study known to this

* On the implicit assumption of total eradication from a state of no control. In practice however the planner is likely to be faced with a decision of a rather more marginal nature: whether or not to expand existing control efforts and, if so, by how much.

writer which has engaged this question (Omer & Ahmed, 1974) isolated significant differences in tolerance to physical activity between a group of infected but clinically asymptomatic subjects and a control group of subjects free of infection — a result which is favorable to the hypothesis*. On the second problem it seems most unlikely that the assumed linear-proportional relationship between physical dysfunction and reduced labor productivity (X_1 in Fig. 2) would in practice exist. The fact that an economy's labor input requirements are highly heterogeneous, ranging along a continuum from intensive physical work effort to intensive mental effort, with intermediate combinations over the range, implies that the extent to which the productivity of labor is actually depressed by schistosomiasis-related physical dysfunction will be highly differentiated (assuming that the impact of infection is confined to labor's physical quality, with no impact on its mental quality). In practice a whole set of functional relationships is likely to exist, and the curves X_2 , X_3 and X_1 in Fig. 2 illustrate some of these possibilities. *A priori* theorising can offer no particular guidance as to the form of relationships, which will vary between specific situations.

The fact that this observation abstracts from the important role played by other determinants of the quality of labor inputs (e.g. residual health status and motivation) and the other cooperant factor inputs with which labor combines in the determination of its productivity in a given activity, reinforces the point. It is important to dispose of the mysterious idea, implicit in these studies, that labor

operates in a vacuum in productive activity. It must be clearly recognised that labor's health status is only one of several complementary inputs to productive activity, together with the availability of capital, land, intermediate inputs and the technology which determines their combination. In specific situations any or all of these complementary inputs may impose constraints which deny the possibility that reduced dysfunction through improved health status will increase the productivity of labor, and so prevent activation of the sequence $S_1 \rightarrow S_2$ for which improved health status may be a necessary, but is not a sufficient, condition. There is no guarantee that improved health status will lead automatically to an increase in labor productivity, least of all in exactly the same proportion.

2. Homogeneous morbidity experience

The difficulty of defending this assumption should be clear from the differential clinical severity gradient which generally characterises the distribution of schistosomal infection within any community. Thus only some of those infected will experience severe disease, the major proportion of infections being fairly moderate or asymptomatic — a fact which highlights the general failure in discussing the economic dimension of schistosomiasis to distinguish between schistosomal infection (indicated by evacuation of ova) and resultant schistosomal disease (indicated by clinico-pathological manifestations). Farooq's (1963) data for the Philippines (see Fig. 3) emphasises the importance of this distinction: 62% of total infections were found

* On similar lines, a World Bank study of Indonesian construction workers found significant differences in Harvard Step Test scores between workers classified as anaemic ($Hb < 11$ g/100 ml, $Hmt < 33\%$) and a random sample classified as non-anaemic ($Hb > 13$ g/100 ml) (International Bank for Reconstruction and Development, 1973, Table 10).

to be asymptomatic while the remaining 38% were distributed in progressively smaller proportions among disease categories 'mild' (21.7%), 'moderate' (14.8%), and 'severe and very severe' (1.5%). In terms of the structure of the hypothesis, this fact considerably reduces the likelihood of transition between S_1 and S_3 (mediated by S_2). In recognition of this differential gradient Farooq (1963) himself employed differential 'loss of working capacity' coefficients (of 25%, 50%, 75% and 100% respectively corresponding to the four severity categories) in his estimate of the economic benefits from schistosomiasis control in the Philippines (an innovation later incorporated into Wright's (1972) global estimate of the gains from control).

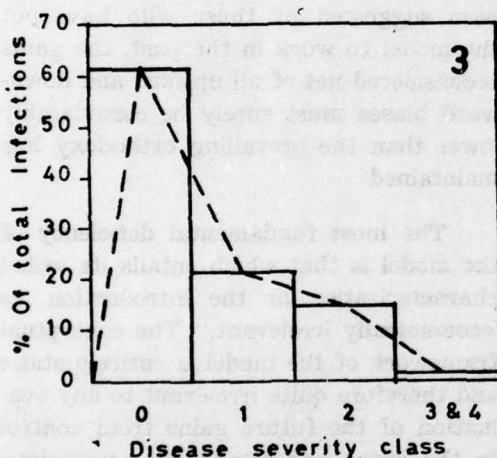


Fig. 3. Distribution of schistosomal infection by severity class of resultant disease as percent of total infections. Source: Farooq, 1963.

3. *Every infected individual is engaged in homogeneous productive activity*

This again is indefensible given known age-sex distributions of infection.

* Defined here as *S. mansoni*, *S. haematobium* and mixed infections.

** This ignores implicit human capital disinvestment occurring through enfeebled scholastic performance of schoolchildren, but whose economic effects are deferred until future labor force participation.

Probably a large proportion of those infected with schistosomiasis will not be labor force participants (children and a proportion of women), and their infections can therefore have no impact on current output. Farooq's (1966) data from the Egypt-49 Project are presented in Fig. 4 to illustrate this point. Of the total sample in the Project Area only 35.9% displayed the presence of schistosomal infection*, and only 53.3% of total infections fell into the category of labor force participants indicated by the shaded area of the distribution (defining the labor force to constitute all males and females in the age group 15-59 yrs). Exclusion of females from the labor force reduces the proportion of those economically active still further to a mere 27.5% of total infections in the sample — compared with the assumption of the model of 100%. In terms of the structure of the hypothesis, this fact severely reduces the likelihood of transition between S_1 and S_3 among the infected population; even if all individuals infected experience dysfunction, economic effects could be manifest only among those economically active**. The assumption of homogeneous productive activity is equally unrealistic. Farooq, for example, was able to allocate his Project Area sample between a total of 12 occupational categories, among which it is probable that significant differences in labor productivity would exist.

4. *Freedom from infection implies perfect health*

It is necessary to validate the transformation of the 'economic loss' model into a 'gains from control model.' While arguably plausible for the relatively

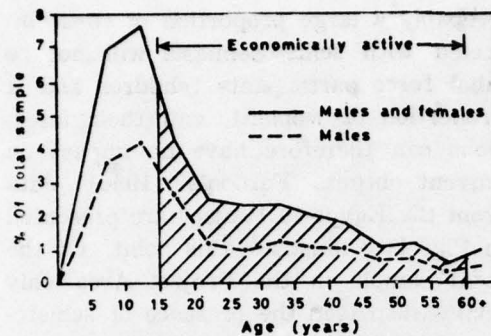


Fig. 4. Distribution of schistosomal infection by age group as percent of total sample in the Egypt-49 project Area.

Source: Farooq et al., 1966, Table 7.

healthy developed countries, the assumption does not transfer easily to developing countries where other debilitating agents are an extensive feature of residual health status. The high prevalence in many developing countries of multiple parasitic infections in combination with poor nutritional intake creates a synergistic disease complex whose effects on labor performance may not be significantly diminished by the elimination of schistosomal infection alone. Thus where multiple infections are common the assumption that schistosomiasis-infected workers would otherwise be healthy will overstate the likely gains from control. Again, the likelihood of transition between S_1 and S_2 is much reduced: insofar as general health status does impose a binding constraint on increased productivity, the constraint may be so dominated by residual health status that elimination of schistosomiasis alone will at best relax the constraint only marginally.

A further criticism of the model is a technical one: the use of average labor product as the output norm for non-infected workers imparts a downward bias to the 'economic loss' estimate which is

directly proportional to the size of α the 'loss of working capacity' coefficient. The bias results from the fact that the measure of the average product of labor incorporates in its denominator all of those who are currently infected and whose productivity is *ex hypothesi* depressed. The problem is that the very measure of output employed as the standard of non-infected output which infected workers will attain after the elimination of their infections (in the simplistic model) is itself dependent on the output levels achieved by infected workers. Rather than an independent indicator of the productivity attainable by any worker, in the terms of this model, it is a misleading composite incorporating a downward bias. Although to this extent, the gains from control are greater than has been suggested by those who have put the model to work in the past, the gains reconsidered net of all upward and downward biases must surely be considerably lower than the prevailing orthodoxy has maintained.

The most fundamental deficiency of the model is that which entails its veiled characterisation in the introduction as 'economically irrelevant.' The conceptual framework of the model is entirely static and therefore quite irrelevant to any evaluation of the future gains from control in the sense understood by economists. The term 'economic loss' is employed by the investigators to describe the resource loss costs imposed on the economy by schistosomal infection, with the implicit suggestion that these are currently borne costs that would be averted and so accrue as measurable benefits in the future if schistosomiasis were eradicated. However if 'economic loss' were reinterpreted as benefits foregone, and the question explicitly reformulated in a dynamic context as «what benefits would accrue to the

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PROCEEDINGS OF THE INTERNATIONAL CONFERENCE ON SCHISTOSOMIASIS --ETC(U)

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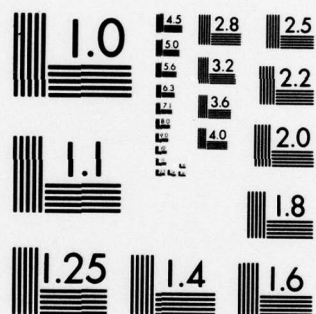
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MICROCOPY RESOLUTION TEST CHART
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economy in the future if schistosomiasis were eradicated?», the whole nature of the analysis would be transformed. This is precisely the question that would be posed by a benefit-cost analysis of the proposed program.

The two features of a benefit-cost analysis which are important here are these : firstly, it is a prospective exercise, requiring analysis of the path taken by benefits and costs over time ; and secondly it requires some specification of the link between the control program input and the economic outputs it generates, in order to be able to attribute benefits and costs specifically to the implementation of the program.

On the benefit side, such an approach would entail critical examination of the age-sex structure of the aggregate morbidity estimate and its occupational profile. Since the productivity of labor varies with respect to age, sex and occupational activity it is manifestly essential to establish what kind of individuals are infected in order to form some idea of its possible importance. If infection is concentrated among skilled workers one would *a priori* expect it to be more important in terms of reduced output than if it affects mostly unskilled workers whose productivity is lower : the output gain from control would be correspondingly higher. Decomposition of the infected population into mutually exclusive subgroups defined by age-group, sex and occupational activity will enable the development planner to identify more clearly the scope of infection and to select target groups from among the infected population on which to concentrate intervention where resources available for control are limited. At the same time, empirical determination of the distribution of infection intensity and the clinical gra-

dient among differential workers categories is a necessary informational requirement given the likelihood that the degree of worker dysfunction caused by schistosomiasis varies significantly with the intensity of infection and the severity of resultant disease. Further, account must be taken of the important fact, noted above, that worker response to schistosomal infection is a function not of schistosomiasis alone but also of residual health status. This is a strategic element in correctly specifying the link between program input and output which underlies any benefit cost analysis, particularly of health sector programs.

Following categorisation of the infected segment of the population in this way, the next step is to assign empirically estimated productivity gains to each worker category isolated in the occupational profile of the morbidity distribution over time — taking account of the time lag between initiation of the control program and its effects on infection. These must necessarily be estimated in the context of the present and future quantity and quality of factors of production, i.e. known resource constraints, if they are to yield informative estimates of the *ceteris paribus* addition to output attributable to schistosomiasis control. It should be clear that measures of the average product of labor have no theoretically obvious role to play in a dynamic evaluation of these output benefits because they reveal nothing about the marginal increment to labor productivity that would result from the elimination of worker dysfunction attributable to schistosomiasis. It may be that labor productivity is already at a maximum given the availability of cooperant factor inputs and the technology for their combination : where this is the case improvement in the physical quality of labor services will

not generate output gains in the absence of supportive complementary measures (e.g. agricultural extension services and farm credit facilities to induce technical change). Here it should be obvious that the benefits of composite packages of this kind cannot be attributed to the control of schistosomiasis alone. Further judgement will be necessary to evaluate additional constraints imposed by institutional phenomena such as the incentive structure of earnings in the relevant sectors, and social norms governing earnings achievement. In short, realistic evaluation of whether schistosomiasis control would in practice generate measurable output gains can manifestly be determined only by realistic assessment of whether the poor quality of labor services resulting from schistosomiasis infection does or does not impose a binding constraint on future output gains in the range of worker categories relevant to the problem.

The key point is this : that, whether the enhanced quality of labour services that results will increase the value of total output, depends critically on what factors, prior to the control program, exert constraints on the expansion of total output. If the quality of labor does not exert a constraint, then no output gains can be expected in the short run. If the quality of labor does exert a constraint which the elimination of schistosomiasis will relax, then output gains are in prospect. In essence the problem is one of estimating the counterfactual — the productivity of labor that will result from a change in the productive environment effected by a change in the prevalence of schistosomiasis through a control program, compared with the actual labor productivity which exists before the change. The assumption of the simplistic macro model considered in this section has been that reduction

in schistosomiasis-caused dysfunction (the 'loss of working capacity' coefficient) would add pro rata to output. In fact however the likelihood of this fortunate event is severely qualified by the existence of many other constraints which intervene in the sequence $S_1 \rightarrow S_5$: those imposed by residual health status, institutional phenomena, resource availabilities and technology.

B. Micro-Analysis

One of the major defects of the simplistic macro-model discussed in the previous section is the total divorce of its estimates of the benefits of control from any empirically validated micro-foundations. Despite the obvious truth that *prima facie* plausibility does not establish empirical validity, the effect of schistosomiasis on the dependent economic variables were simply assumed. Yet it is precisely these linkage relationships whose nature and importance need to be objectively determined prior to evaluation of the gains from control. In an effort to cast empirical light on this question four studies have been undertaken which have sought, through comparison of the performance of infected and uninfected labor, to isolate the nature and size of any infection generated differential in economic variables that may *ex hypothesi* be expected to occur (assuming the hypothesis of Fig. 1).

The first study, carried out by Foster (1967), concerned an irrigated sugar estate in Tanzania over the period 1962-3. Taking an experimental sample of some 200 young male cane-cutters and 200 young male irrigators (among whom workers stool-positive for *S. mansoni* infection formed the comparison and those stool-negative the control group). Foster investigated their relative performance with respect to three variables upon which

schistosomiasis could be expected to exert influence. The first variable, static health status, was determined using simple haematological and anthropometric indicators. The second variable, dynamic health status was examined in terms of differential morbidity experience, determined by a series of indicators of the frequency and duration of out-patient and in-patient hospital attendance. The third variable, labor performance, was investigated in terms of differential levels of labor absenteeism and output per shift over the study period (values for the latter were obtained only for the cane-cutter category).

The results suggested that schistosomiasis did not influence the first variable: mean haemoglobin, body weight, and height values for infected workers were not significantly* different from those observed for the control group. Dynamic health status, however, did display some sensitivity to schistosomal infection. While values for infected and uninfected workers as a whole were not significantly different, disaggregation revealed interesting differences. In terms of out-patient treatment, only the mean value of attendances per individual was significantly higher for infected than for uninfected cane cutters, whereas infected irrigators displayed significantly higher mean values for all indicators, except number of conditions diagnosed, than their uninfected counterparts. A similar pattern was apparent in the inpatient series. Only the mean value of hospital days per individual was significantly higher among infected than uninfected cane-cutters, while infected irrigators experienced higher mean values for the per-

centage admitted to hospital, hospital days per individual, and the number of conditions diagnosed per individual. *Prima facie*, these results support the hypothesis that schistosomiasis is responsible for greater morbidity than normal, the size of this effect being a positive function of infection intensity: irrigators experience greater occupational exposure to water contact and therefore confront a higher probability of acquiring intense infection than cane-cutters. Labor performance results revealed that mean monthly work-shifts lost for both cane-cutters and irrigators were significantly higher among infected workers as a whole, although disaggregation showed this difference to be significant only for irrigators. On the other hand, values observed for mean output per shift in each of two grades of canefield work displayed no statistically significant difference between infected and uninfected workers. Thus, while the flow of labor services appeared to be negatively related to schistosomiasis, the quality of that flow in terms of output per unit of time was not observed to be sensitive to the disease. The implications of Foster's study are that schistosomiasis does seem to impose direct resource use costs in the form of expenditure on the treatment of infected labor, and indirect resource loss costs in the form of foregone output. The latter arise only as a result of the observed contraction in the flow of labor services associated with absenteeism and not from any degeneration in its quality; it is unclear, however, to what extent the indirect costs of absenteeism in fact represent the (foregone labor-time) opportunity costs entailed in the delivery of treatment to infected workers**.

* 95% confidence level.

** A confusion whose clarification would be necessary to avoid double-counting of benefits in a benefit-cost analysis of a control program.

A second study, undertaken five years later on the same estate by Fenwick & Figenschou (1972), selected bonus earnings (a function jointly of the number of days worked and physical product per day) as the dependent variable for observation as a proxy measure of the physical productivity of labor. Hypothesising that stabilisation of the labor force had exposed it to infection for a longer period of time and that it had in consequence developed more intense infections than those encountered in the previous study, the expectation of these investigators was that schistosomiasis would manifest more serious implications for labor productivity. Retrospective comparison of the bonus earnings of cane-cutters infected with *S. mansoni* with those of uninfected controls in each of a consecutive series of six-month time periods* gives strong *prima facie* support to their hypothesis: mean bonus earnings achieved by uninfected workers were consistently higher in each period. Observed differentials were 11.0%, 11.4%, 6.0% and 13.7% respectively (the three highest values are all statistically significant**). Reinforcing the implications of these data, longitudinal analysis of the bonus earnings performance of an additional group of infected workers over the year 1969 showed a dramatic improvement of 28.11% after chemotherapy. Pre-treatment earnings of this group had been 12.5% less than the controls, while post-treatment earnings narrowed the shortfall to only 6.5%. Further the likelihood that perhaps 30% of the treated group failed to respond to

chemotherapy underscores the apparent sensitivity of labor productivity to freedom from infection. To transform these bonus performance values into measurement of physical product, the investigators generalised a 4:1 ratio*** between bonus earnings and the quantity of cane cut to each of the study periods, indicating physical product differentials of 2.75%, 2.85%, 1.5% and 3.4% respectively — or a mean differential of some 2.6% between the physical productivity of infected and uninfected workers§.

The third study, carried out by Gateff et al. (1971) in Cameroun, again on a sugar estate, attempted assessment of the influence of infection with *S. haematobium* on a series of five dependent labor performance variables. The investigators obtained values for the mean number of days per week on which (1) a cutting bonus was earned (2) a weeding bonus was earned (3) no bonus was earned (4) the basic work task was not completed and (5) complete absence from work occurred. The first four indicators relate to labor productivity and the fifth to labor supply, the *ex hypothesi* expectation being that the first two would be negatively associated and the remaining three positively associated with the presence of schistosomal infection. Longitudinal evaluation of the sensitivity over time of the dependent work variables to changes in the status of the schistosomiasis variable among three groups of male workers, aged 18-25, failed to elicit support for any

* January 1968 through December 1969.

** 95% confidence level.

*** Observed over the first six-month period of 1969.

§ Since the transformation relationship was estimated for a period of poor cutting conditions, the investigators suggest that in normal circumstances the differential would be nearer 5%.

● An uninfected control group, and an infected group randomly divided into two subgroups — one of which received chemotherapy, and the other, together with the uninfected controls, a placebo.

of these 5 hypotheses. In none of the cross-section series determined for the study sample at intervals of 2, 3 and 4 months after treatment was any statistically significant differential observed on any one of the set of performance indicators among any of the groups involved, with a single exception: the two-month cross-section disclosed that treated workers achieved a much lower value than either of the other two groups for the mean number of days of uncompleted work. Although this phenomenon may have represented a response to freedom from infection, the fact that it was not maintained in the remaining series suggests that its occurrence was probably due to some other factor. Given the otherwise uniform performance of all groups on the set of dependent work variables the conclusion is inescapable — that on this estate no significant role can be attributed to schistosomal infection in the determination either of the supply of labor or of its productivity.

The fourth study, carried out by a multidisciplinary research team (including economists, for the first time) unquestionably constitutes the most serious and well-designed effort yet undertaken to investigate the hypothesised linkage between parasitic infection and economic variables (Weisbrod et al., 1973, 1974; Baldwin & Weisbrod, 1974). Proceeding from the general hypothesis that schistosomiasis (together with four other parasitic infections*) is a debilitating infection responsible for a reduction in both the quantity and quality of labor. Weisbrod et al. (1973) employed multiple regression analysis to evaluate four corollary hypotheses using data relating to agricultural workers on the Geest banana plantation

in St. Lucia, in each case regressing the dependent variable on a common set of infection and other independent variables (age, education, etc.). Assuming a simple additive relationship between each disease and the dependent variable, the *ex hypothesi* expectation was that in each case statistically significant negative coefficients would show up in the estimated regression equations for each of the dummy infection variables. The results for schistosomiasis *mansoni* are summarised in Table 1.

The first hypothesis, that schistosomal infection reduces worker productivity as a result of its debilitating effect, was tested with earnings per week as the proxy dependent variable for labor productivity. Results for both the quantitative and the qualitative models (the latter decomposed the schistosomiasis variable into low egg count**/light infection and high egg count/heavy infection) failed to reveal any significant association between the presence of infection and weekly earnings. While some of the estimated coefficients for the schistosomiasis variable entered with the anticipated sign, its distribution by sex and infection intensity category displayed no consistent pattern. Nevertheless, since labor productivity as measured by weekly earnings is a function both of labor productivity per day, itself dependent on the nature of work performed, and on the number of days worked per week, this result may well have reflected the lower productivity of infected workers who had shifted to less demanding but less productive work. The investigators therefore took as their second hypothesis the proposition that infection causes workers to opt for less intensive work in order to minimise the

* Ascariasis, trichuriasis, strongyloidiasis and ancylostomiasis.

** < 19 eggs/g faeces.

TABLE 1. Possible effect of schistosomiasis on workers in a banana plantation in St. Lucia.*

Hypothesis	Dependent variable	Additive model regression coefficients for schistosomiasis variable			
		Qualitative model		Quantitative model	
		Males	Females	Males	Females
1. Infection reduces weekly earnings	Gest worker earnings per week in E.C.* cents	-105 (146)	22 (89)	F -144 (143) M 20 (141)	24 (118) -54 (99)
2. Infection causes worker to shift to less demanding work	Task days worked as percentage of total days worked for persons performing task jobs on at least 10% of days worked	—	—	F -0.003 (0.058) M -0.04 (0.06)	-0.05 (0.11) 0.008 (0.09)
3. Infection reduces marginal productivity of labor	A. Earnings per day worked in E.C.* cents	—	—	F -86** (42) M -80*** (41)	13 9 -4 (16)
	B. Earnings per day on specific task jobs in E.C. cents	—	—	—	—
	Task a	64 (275)	-43 (35)	—	—
	b	—	34 (72)	—	—
	c	-71 (228)	32.1 (16.5)	—	—
	d	-69 (106)	—	—	—
4. Infection causes worker to work fewer days per week	Mean days worked per week	—	—	F 0.43 (0.53) M 1.12** (0.53)	0.04 (0.74) -0.16 (0.62)

* Source: Weisbrod et al., 1973

** Significant at 0.05 level

*** Significant at 0.10 level

E.C. East Caribbean

F = Few schistosome eggs in stool

M = Many schistosome eggs in stool

a = Carrying bananas from field to loading point

b = Wrapping banana stalks - performed only by females

c = Planting banana plants

d = Digging drainage canals - performed only by males

disutility of physical work effort associated with infection. This regression employed the ratio of days worked at task work to day work over an 18-month period as the dependent variable, the former being considered to involve more intensive work than the latter and therefore less likely to be chosen by infected (and *ex hypothesi* debilitated) workers. Again, however, while the regression coefficients showed up with negative signs for all categories except high egg-count females, none were significant in explaining the observed variation among workers in the percentage of task work performed over the study period. The third hypothesis, that infection reduces the productivity of labor, was separately analysed with a group of regressands: daily earnings in general (at all types of task and day work) and daily earnings for four different types of task work. The regression disclosed that schistosomiasis was significantly related to lower global daily earnings among male workers, implying a substantial reduction of some 30% in average daily earnings. But despite this valuable support for the hypothesis that schistosomiasis does act to depress labor productivity, no such association was observed among female workers. Nor was the effect consistently distributed by worker category over all types of task work — indeed the schistosomiasis coefficient entered as significantly positive for daily female earnings at one of the task jobs (planting banana plants). Regression analysis of the fourth hypothesis, that infection causes workers to work fewer days per week (again, in order to minimise the disutility of work effort), even if it does not reduce actual productivity at work, yielded a quite different result. Instead of taking the anticipated negative sign, the heavy infection schistosomiasis coefficient appeared as significantly posi-

tive for male workers; but while the same coefficient was (barely) negative for female workers, the light infection schistosomiasis variables were also related positively (though not significantly) to days worked per week by both sexes.

Taken at face value nothing very clear emerges from these studies. Neither Foster nor Gateff found any evidence that schistosomiasis could be held to depress the productivity of labor, while both Fenwick's and Weisbrod's results suggested the existence of a significant linkage between these variables. On the other hand, Foster's analysis suggested a significant negative linkage between schistosomiasis and labor supply resulting from the greater morbidity to which infection predisposes — a relationship which is not manifest in either Gateff's or Weisbrod's studies. Indeed the latter implies the reverse — for reasons moreover of rational economic choice rather than physiological determinism.

The failure of these studies to provide conclusive evidence concerning the nature and size of the linkages between schistosomiasis and economic variables in itself argues the case for further research to establish the micro-foundations of estimates of the benefits of control. Their inability to resolve unambiguously the effects of schistosomiasis prevents the development planner from making any sensible prediction of the outcome of contemplated intervention programs.

In general, no effort has been made in these studies to determine the intensity of infections (S_1) nor the severity of resultant schistosomal disease (S_2) nor the extent of dysfunction (S_3) imposed by the initial schistosomal infection in the samples investigated. The focus of these efforts has been merely to relate the pre-

sence of schistosomal infection (S_2) to dependent economic variables (S_5) without attempting to investigate the underlying structure of causal sequences; $S_1 \rightarrow S_2$, $S_2 \rightarrow S_3$, $S_3 \rightarrow S_4$, $S_4 \rightarrow S_5$. The significance of this fact is critical: it accounts for much of the uncertainty surrounding the specific results and the possibility of their generalisation. To take the dominant extreme where no relationship $S_1 \rightarrow S_5$ is observed, the reason must be that the underlying sequence is not activated — but where does the sequence break down? The structure of the hypothesis suggests four competing explanations. **First**, $S_1 \rightarrow S_2$. None, or very few, of the infections sampled are intense (indicated by 'high' egg counts) which precludes activation of any of the remaining sequences in the causal chain. **Second**, $S_2 \rightarrow S_3$. The range of schistosomal infections is relatively intense, but individuals in S_2 do not progress to the state S_3 in which they manifest schistosomal disease. Weisbrod et al. (1973) plausibly suggest that breakdown at this stage in the sequence may be attributable to physiological compensation which imposes a threshold below which infection is insufficiently intense to have any further effects. **Third**, $S_3 \rightarrow S_4$. The infections sampled are sufficiently intense to cause resultant disease, but this is insufficiently serious to impose significant dysfunction. Again, Weisbrod's suggestion of a non-linear relationship between infection intensity and further effects may account for inactivation of this sequence. **Fourth**, $S_4 \rightarrow S_5$. The dysfunction imposed by schistosomal infection alone is insufficiently serious to affect economic variables. This may occur for either or both of two reasons: because of constraints internal to the infected individual, such as residual health status, education

and motivation*, or because of constraints external to the infected individual in the productive environment — those imposed by resource availabilities and technology. These considerations furnish an interpretation both of the specific results of the empirical studies and of the degree to which they can be generalised to situations other than those specifically investigated. Given the absence of any information concerning the intervening sequences in these studies, each case where no relationship has been observed between schistosomal infection and a dependent economic variable can be rationalised in terms of any one of the four possibilities of breakdown elaborated above. This applies to Foster's finding that schistosomiasis exerted no apparent impact on the productivity of cane cutters; to Gateff's failure to observe any significant linkage between schistosomiasis and either the supply or the productivity of labor; and to Weisbrod et al.'s observation that schistosomiasis did not affect the choice between physically intensive and less intensive work (task and day work).

What can be said of those results which have exhibited significant association between schistosomiasis and economic variables? Foster's finding that infected irrigators experienced significantly higher absenteeism than their uninfected counterparts and infected cane workers is certainly open to question: the implicit hypothesis that the relatively high intensity of infection among irrigators predisposed to abnormal morbidity which in turn resulted in higher absenteeism is not sustained without empirical comment on the distribution of infection intensity between sample categories. Interpretation of Fenwick's finding of a negative association between Bonus earnings (assumed

* Weisbrod et al. (1973) cite "...the intervention of socio-cultural variables."

to proxy labor productivity) and infection itself turns on interpretation of Foster's conclusion. Since bonus performance depends jointly on both labor supply (days worked) and on labor productivity (physical product per day) the conclusion that schistosomiasis depresses productivity may not be the appropriate one: it seems quite possible that the differential bonus performance resulted from a reduction in labor supply activated in the manner suggested by Foster's analysis. But the absence of information concerning the separate behavior of labor productivity and labor supply in the sample, and of control for other explanatory variables such as age, cutting experience, grade of field worked, infection intensity and residual health status, prevents resolution of these alternative interpretations. Weisbrod et al.'s results for their first, third and fourth hypotheses call for more detailed comment. The test for the third hypothesis is the first to have unambiguously isolated a negative relationship between infection and daily labor productivity (at least for male workers) — the first (and only) suggestion in existing empirical work that the full sequence implicit in the hypothesis is activated. Further, the test for the fourth hypothesis revealed a significantly positive linkage between schistosomiasis and labor supply (days worked per week) — contrary both to previous empirical results and to *ex hypothesi* expectation. Nevertheless, as the authors explain, the phenomenon is easily understood in terms of the strong income effect of infection generated depression of labor productivity in order to maintain target weekly income: a behavioral response which entails utility costs in the form of foregone leisure for infect-

ed labor. Or it could equally well reflect the fact that those who work more anyway are more likely to develop intense infections in consequence (indicating either a reciprocal or an asymmetric relationship contrary to that usually assumed). But the attraction of the former hypothesis (that more days are worked per week, at least by males*, to overcome the income loss imposed by dysfunction) is that, in conjunction with the lower labor productivity of infected males implied by results for the third hypothesis, it helps to explain the neutral result obtained for the first hypothesis. Thus schistosomiasis, at least for males, appears in this study to reduce the quality of labor services — but the income-effect stimulus to expansion of labor supply means that no total output costs are incurred. Nevertheless, avoidance of these resource loss costs is achieved only at the welfare cost of reduced leisure. The implication is that while control of schistosomiasis would not yield any output gains, it would yield a direct welfare gain in permitting increased leisure. The special significance of this result is twofold. It should help to dispel the deterministic notion, implicit in the macro-studies, that impaired productivity necessarily leads to a reduction in total output. And in addition it points up the distinction between an 'economic' effect (on output) and a 'non-economic' effect (on leisure), both of which would be incorporated into a benefit-cost analysis of a control program (in the former case the gain would be zero, in the latter positive). Nevertheless, later results (Baldwin & Weisbrod, 1974) indicate that the significant negative association between schistosomiasis

* Which is consistent with the male's role as the most important wage earner in the family unit.

and daily productivity, and the positive association between schistosomiasis and labor supply, both disappear (the latter relationship is reversed) — which reopens the field of interpretation to the four possibilities for inactivation of the causal chain elaborated above.

The variety of the associations and non-associations between schistosomiasis and economic variables which have emerged from these studies, and the diversity of interpretations which can be offered to account for them, leave nothing about which to generalise: except that the nature and size of the economic consequences of schistosomiasis remain unclear. However, although the sanguine assumption of substantial output losses associated with schistosomiasis, which have formed the basis of macro-estimates of the gains from control, have clearly failed to secure empirical support, this does not preclude the possibility that schistosomiasis may in other, as yet untested, environments exert a substantial economic impact. *Prima facie*, two considerations suggest that the results obtained err on the low side of the true range of effects in infected communities. The first is that the focus of each of the four studies on controlled work environments (three sugar estates and one banana plantation) inevitably excluded from their samples workers whose dysfunctional experience in response to schistosomiasis was sufficiently great to deny them entry into the workforce investigated. For this reason self-selection of samples may have led to failure to capture the more serious economic consequences of schistosomal infection. The second consideration is that the range of infection intensity sampled in each of these studies may have been insufficiently great to result in substantial effects on economic variables. Both the controlled nature of the work environ-

ments under study, and the relatively mild intensity of infection prevalent (in St. Lucia, at least) lend support to this hypothesis.

Conclusion

The problem of identifying the linkages between schistosomiasis and economic variables, and of valuing the benefits that would accrue from control, is one of considerable complexity. The complexity of the issue is inevitable. It results essentially from the fact that health programs are merely permissive: they furnish one of the conditions for an increase in labor productivity (for example) without being its sufficient condition, or even a necessary condition. Nevertheless the need remains for health sector programs to demonstrate the legitimacy of their claims on scarce developmental resources within a benefit-cost framework.

Existing research has failed to provide the development planner with the information necessary to predict the economic outcome over time of programs of schistosomiasis control. The macro-estimates of the gains from control have assumed that schistosomal infection substantially impairs the productivity of labor and that its elimination would lead to equally substantial productivity gains — an assumption which does not receive empirical validation in the micro-studies. Further, they have generalised these benefits to the whole of the infected population without regard to its composition by age, sex and occupational activity, or to the clinical gradient of schistosomal disease, and have assumed them to accrue instantaneously and to be additive over time. These conceptual inadequacies have stemmed from a failure to appreciate the causal sequences which underlie any linkage between schistosomiasis and economic

variables, and therefore the factors which influence the likelihood that schistosomiasis will manifest economic effects. Inattention to the basic structure of the hypothesis has distracted attention from the need to decompose the infected population into differential productivity subgroups and to define the distribution of disease severity among them. Equally it has yielded empirical research whose inconclusive results may well be attributable to the mild intensity of schistosomal infections sampled. The most urgent requirements for future work are therefore twofold. In areas where control activities are contemplated, detailed information needs to be gathered regarding both the age, sex and occupational profiles of schistosomal infection, and of the distribution of disease severity (or at least its proxy, infection intensity) among the subgroups so defined. At the same time further

micro research should focus on areas where prior expectation of significant economic effects of infection is greatest — in other words where observed disease severity is very high. Results of such research should at least establish an upper bound to assumptions about the economic effects of infection which feed into predictive models to estimate the economic benefits of intervention.

These suggestions are offered not as a counsel of perfection but as a pragmatic strategy. Only when such refinements are achieved will it become at all possible to make any sensible prediction of the future economic outcome of control programs. And not before this is achieved does it seem likely that schistosomiasis control will be allowed to make its most appropriate contribution to the promotion of developmental objectives.

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THE SNAIL INTERMEDIATE HOSTS OF SCHISTOSOMIASIS IN LIBYA WITH SPECIAL REFERENCE TO THEIR ECOLOGY

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The Libyan Arab Republic covers a territory of 1,760,000 km² of mostly desert land, the area suitable for human habitation being estimated at no more than 8% of the total. Although the territory is twice as large as Egypt, the population was recently estimated at about 2 million only. The main feature of the Libyan population is that about half the population is under 15 years of age.

The present report is the result of an intensive investigation made in the course of a World Health Organization assisted project and covering a period from July 1969-July 1971. During this time the senior author was the WHO Expert. National establishments dealing with bilharziasis did not exist. Accordingly, the senior author started surveying for infected individuals and vector snails with the assistance of Dr. Hind I. El-Gindy. Permanent units were established to continue and follow up the work.

To our knowledge the first case of urinary bilharziasis together with its snail host was detected in 1925 (Durand, 1926) in the south of the country at the Algerian border close to Ghat. To screen infected persons and locate the snail intermediate hosts it was necessary to travel over distances totaling about 30,000 km

over rough roads. In the 2-year period 33,959 persons were examined and 1976 (6%) cases of either urinary or intestinal bilharziasis were found.

Historical Review

Zavattari (1931) reported the presence of urinary bilharziasis in Fezzan in south-western Libya. Lodato (1932) discovered *Bulinus truncatus* and described a few cases of urinary bilharziasis from Disa (Ubari, Fezzan). Many cases were found by Andolfato & Fedeli (1934) in Marzuk, while Ghat was incriminated as a focus by Giordano (1935). Cases were detected by Impallomeni (1937) in Brak. Casati et al. (1938) were the first to undertake a mass survey in Fezzan. Another mass survey was carried out by Nastasi (1938) in the Sebha, Ubari, Shati, Marzuk and Ghat Districts of Fezzan. He indicated the foci of infection and snail sites and was the first to report on the presence of *Biomphalaria* in Ghat.

The presence of a snail identified as «*Physopsis africana*» was reported by Boscardi (1943) at Sebha, Brak and Gira. Another comprehensive mass survey was carried out by Vermeil et al. (1952). They recorded the location of infected cases and indicated sites for *Bulinus* snails. Moreover, they verified the presence of *Biom-*

phalaria snails in Ghat and raised the problem of endemicity of intestinal bilharziasis in Ghat.

Berry (1963) reported *Bulinus truncatus* in Dabbusiah spring (50 km west of Derna on the Mediterranean coast). Hamami (1965) verified the endemicity of urinary bilharziasis in Derna and collected many snails from the same spring. Halawani (1966) found *Bulinus* snails only in water pools near the spring.

Berry (1963) also visited Sebha and reported two distinctive species of *Bulinus*, one in Sebha and one in Brack. Later, Halawani (1966) and Yasuraoka (1966) made a good survey for infection and snails in Fezzan. Infection was detected in Sebha, Shati, Ubari and Marzuk Districts and they encountered snails in Sebha and Marzuk Districts. Dursoir (1967) reported positive cases from Gragra, Berket, Mahrouga, Gedid (Sebha) and Traghen and snails (unidentified species of *Bulinus*) in Sebha, Semno and Marzuk.

Müller & Fauga (1952) again pointed out the presence of *Biomphalaria* snails in Fezzan. Mansonian bilharziasis was first reported from Taourga (a marshy area of about 180 km² south of Misurata, Tripolitania) by Goodwin (1957). The snail intermediate host was collected from the spring by Berry (1963) and termed *Biomphalaria*. Later Halawani (1966) and Yasuraoka (1966) identified it as *B. alexandrina*.

Observations and Discussion

Three main distribution areas have been ascertained for bilharziasis in the Libyan Arab Republic. Although previous investigators have reported cases and snail vectors outside these above mentioned areas and the present survey has

also detected infected persons in isolated zones in the desert, neither time nor staff were adequate for exploring the subject any further.

1. Derna focus of *Schistosoma haematobium*

A circumscribed focus for urinary schistosomiasis is confined to Derna city which lies on the coast of the Mediterranean in the east, about 300 km west of the Egyptian border, and which can be considered as an extension of the Egyptian focus. The first cases were reported in 1955 and up to 1970 about 130 cases had been detected in a period of 15 years. In the present investigation about 7228 persons were examined in a period of a month and 285 (4%) were found to pass *S. haematobium* eggs.

The water supply of Derna is derived from two springs each giving off a main water stream, running on opposite sides of a valley. The western water system is most surprisingly free from the snail vectors, while the eastern system, deriving from Bilad spring, is infested with *Bulinus* snails and is responsible for the bilharziasis infection in Derna City.

Around the «Bilad» spring, water gushes from the mountain and then runs at the bottom of the valley in a shallow stream with a sandy substratum and a heavy growth of aquatic plants consisting mostly of *Potamogeton americanus* and *pectinatus*. Just south of the city water is led to the gardens and fields in the western and northern outskirts of the city through covered cement tunnels passing under the stream. The «Bilad» stream forms pools in its course, which were found heavily infested with *Bulinus* snails. Snails were also collected from inspection chambers interrupting the tunnel system, clinging to cement walls but only

shells could be obtained from open branches in the field. In March 1971 large numbers of egg-masses were found on the broad leaves of *Potamogeton americanus* together with numerous juvenile snails, 1 mm high, which denotes that the breeding season occurs in spring while the collection of large size snails in June marked the end of the spring breeding season.

The morphology of the shell as well as the internal anatomy of the viscera confirmed that the snail is *Bulinus truncatus* which is the dominant species in North Africa. Its short spire places it close to the old «contortus» type.

Search for this snail in 'Ain Mara and 'Ain Dabbusiah, in which it had been reported before, revealed the complete absence of *Bulinus* in both places, although the conditions appeared suitable for snails in the former spring, whereas the pumping of all the water in Dabbusiah spring has left no pools in its vicinity to support any colony of snails.

Other aquatic snails found in conjunction with *Bulinus*, specially in the stream, were *Planorbis planorbis*, *Gyraulus mareoticus*, *Succinea cleopatrae* and *Bythinia tentaculata*. The stream was freed of snails with only 2 kg of Bayluscide.

2. Fezzan focus of *Schistosoma haematobium*

This wide area stretching over a length of 1000 km in the south west of the country consists of six valleys collectively known as Fezzan. The valleys are mainly chains of oases.

In 1971 the population was estimated at some 121,700 persons. These are a mixture of different races, as the oases

were lying at the cross-roads between the Nile Valley and the Atlantic Ocean on the one hand, and the Mediterranean and African Savannah on the other hand. The inhabitants thus are a mixture of Arabs, Berbers and Negroes. Clearly there have existed opportunities for the importation of disease from their countries of origin.

a) The northern valley (Gufra) is practically free of human infection, probably due to the high salt content of the water which makes the habitat unsuitable for freshwater snails. Only one focus for urinary bilharziasis lies deep in the desert in the east. Water gushes from a high hill in the village, runs in tunnels under the houses and collects in the village in a pool which harbors numerous *Bulinus truncatus* snails.

b) The second valley, Bouanis, draws its water supply from deep wells from which it is lifted by mechanical pumps. The water collects in cement reservoirs and is distributed by cemented channels. *Bulinus* snails were encountered in deep wells in Semno as well as in cement reservoirs and channels.

The infection among the population is higher to the south and diminishes northwards. Two types of *Bulinus* snails were encountered in this valley, the low-spined *contortus* type and the extremely long-spined *innesi* type, which almost resembles a broad *Bulinus* (*Pyrgophysa*) *forskali*. Both types of *Bulinus* were found infected with human type schistosome cercariae.

Characteristic ecological features of the snail habitats in this valley are the following :

1. The older the water reservoir, the more liable it is to infestation by snails. Reservoirs built in the last 4 years were seldom found infested.

2. Water from which snails were collected was soft, sweet and almost clear; usually it was shaded.
3. Reservoirs cleared periodically were negative for snails, while those with standing water and a heavy growth of algae were occasionally found infested, specially deserted ones.
4. No snails were found in sandy shallow reservoirs.
5. There are two breeding seasons: one in spring, with many egg-masses by the end of February and juvenile snails in March and an autumn season with egg-masses in August and juveniles appearing at the end of September.
6. No infected snail was found until the June 2nd and the last snail collected was on December 28th. In mid-summer the death of infected snails marks a drop in the rate of snail infection with larval stages. The percentage rises in the autumn months, with new infection appearing in middle sized snails. With a drop of temperature below 10°C in winter, the brunt of the infection appears in old snails. The transmission season lasts about 5 months, as no water contact is expected in November and December.

c) In El-Shati Valley, with low level land, the infection in the human population is restricted to the east (the valley is 140 km long). Snails were typical *Bulinus truncatus* (contortus type). These snails disappear westward where the water assumes a reddish coloration, probably due to iron deposit. Snails in this valley inhabit wide marshes and pools.

d) In the Adjal Valley, the infection is spotty, *Bulinus* inhabits marshes, pools,

springs and in one particular place the *Bulinus*, with their short spire, smooth shell, round shoulder and large size, at first give the impression of being *Bulinus* (*Physopsis*), but there is no collumellar truncation. This valley has infected villages without snails and *vice versa*.

e) In Hufra Valley, snails were collected from shallow water oozing out of the ground. In one town, Tragen, many wells harbored several living *Bulinus*. In one spring plenty of shells were found, but an exhaustive search failed to reveal living snails. It is possible that snails sink deep in low water to avoid salinity on the surface but show a different picture in high water.

Ghat district is interesting on account of the presence of both snail vectors of bilharziasis. *Bulinus truncatus* had disappeared from the old sites it had been reported from and had reappeared in new water channels, with a concomitant high prevalence of human urinary bilharziasis. Only one shell of *Biomphalaria alexandrina* was detected in a flooded grassy area, while plenty of *Biomphalaria pfeifferi* were collected from a spring. All of them were free from schistosome cercariae and examination of more than 200 stools did not reveal *S. mansoni* infection. This is the northernmost distribution for *B. pfeifferi* in the Middle East.

f) In Wadi El-Hekma on the way to Chad and Niger, infection with *Schistosoma haematobium* is high in Gatroun and associated with *Bulinus* of the «contortus» type. In general, 4 types of *Bulinus* were encountered the contortus type, the innesi type, the form somewhat resembling *Physopsis* and another with a deflected opening. All proved to harbor schistosome cercariae.

3. Misurata (Tauorga) focus for *Schistosoma mansoni*

The third focus for bilharziasis is situated 240 km east of Tripoli and 50 km south of Misurata town. It is a dangerous focus for intestinal bilharziasis. The area is inhabited by 31 tribes with a total population of 16,000 persons.

The main water supply in Tauorga is a large, old, warm water spring from which originates one main stream and a few small canals. They branch into streams that end in marshes. *Biomphalaria alexandrina* were collected in large numbers from the shallow borders of the spring, from the streams and marshes. The infestation with snails is higher, the nearer a village is to the old spring.

The water originates at a depth of 300-400 m, it maintains a temperature of 31-32°C in August and was also warm in winter time.

The rate of infection in school pupils was 18%. In a sample covering 25% of the population it was 24.7%, a high rate presumably due to repeated exposure. One school close to the spring, examined twice, revealed a 96% infection. In general the nearer a village was to the spring, the higher the infection rate.

The ecology of these snails proved interesting. They accumulate near the periphery and around plant mats roofing some of the water surface in the spring.

In the summer time they thus avoid the hot rays of the sun by being under the heavy cover of the dead algae forming a ceiling over the shallow streams, while in winter time they drop to the bottom of these streams.

They were seldom collected from palm-leaves in the water but were readily found on the peduncles that had formerly borne ripe dates.

Plants accompanying *Biomphalaria* in its habitat are *Juncus algae*, *Scirpus*, *Chara*, *Zanichiella*. Snails die on the periphery of the marshes where the salinity is higher.

Out of 431 snails collected on the 3rd of November, 3 harbored human type schistosome cercariae. Other trematode cercariae encountered were cystophorous, echinostome and strigied cercariae.

Another area with *Biomphalaria* snails was detected 100 km south of Misurata. *Biomphalaria alexandrina* were collected from the sweet water springs but not from the brackish lakes. Examination of school children revealed no infection as people do not pollute the sweet water of the spring which they use for domestic purposes. They use the brackish water bodies for swimming and other purposes.

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INCIDENCE AND PREVALENCE OF *SCHISTOSOMA MANSONI* IN THE GEZIRA SCHEME, SUDAN

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Dr. Amin will introduce the Gezira irrigated area of the Sudan in his paper to be read in the plenary session dealing with molluscicide control of vector snails. I want briefly to describe the work being undertaken to assess the control measures from the epidemiological viewpoint and to relate the results to date.

I must stress the preliminary nature of these results, since the assessment has been conducted for 21 months only, and a true indication of what is occurring cannot really be expected for about four years.

The assessment has been based on stool examination since no immunological test was considered reliable enough. A thick smear technique was chosen after comparison of three methods: the Bell filtration method, the digestion method,

and a modification of the Kato thick smear technique. This technique differs from the Kato technique in that thick glass coverslips are used instead of polyethylene or cellophane. The glass allows pressure to be applied to the sieved stool sample on a microscope slide in such a way that there results a thin layer of stool in which the eggs are amongst the largest particles. With the light adjusted correctly the eggs appear as transparent objects under the microscope and are easily visible under low power ($\times 40$). If eggs are not clear, they may be rolled over to expose the spine by moving the coverslip; or they may be viewed under higher power ($\times 100$). Scanning is done at $\times 40$ magnification.

Initial prevalence studies indicated that villagers, though keen at first to be examined, soon became unenthusiastic when asked for further re-examination, and there would be too large a proportion who would not cooperate in subsequent re-examinations. Evaluation was therefore based on incidence and prevalence rates in younger school children, aged 7-10 years.

However, as can be seen from Table 1 and Fig. 1, prevalence of the disease was so high in these children that there were too few children found negative to constitute sufficient numbers to make up negative

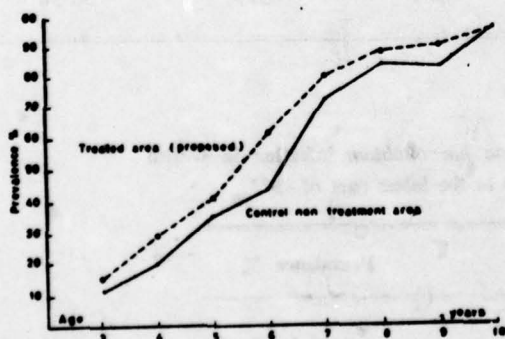


Fig. 1. Incidence of *Schistosoma mansoni* infection in Gezira school children at beginning of assessment period.

cohorts for future examinations in incidence studies, unless a very large number of schools were included in the study. The personnel required for this work was not available and, instead, it was decided to investigate the 3-6 year old pre-school children in certain villages to help make up the negative cohorts. It is important

to note that prevalence was higher in the area where chemical control (by Frescon) was to be applied.

Schistosoma haematobium infection tended to be focal and generally very much less prevalent than *S. mansoni* infection and was not included in the assessment (Table 2).

TABLE 1. Prevalence of *Schistosoma mansoni* infection in Gezira children aged 3-10 years at the beginning of the assessment period.

Area	Age yrs	No. examined	No. positive	Prevalence %
Proposed treatment area	3	102	12	11.76
	4	107	32	29.90
	5	114	48	42.11
	6	145	89	61.38
	7	346	277	80.06
	8	334	293	87.12
	9	309	277	89.64
	10	87	83	95.40
Totals		1544	1111	71.96
Control non-treated area	3	112	12	10.71
	4	108	21	19.44
	5	92	32	34.78
	6	121	57	47.11
	7	132	95	71.97
	8	122	101	82.79
	9	140	114	81.43
	10	87	83	95.40
Totals		914	515	56.36

TABLE 2. Prevalence of *Schistosoma haematobium* infection in Gezira children age up to 10 years in the latter part of 1973.

Village	Prevalence %
Bint El-Hag	14.6
Azrag	0.8
El-Sereiha	12.2
El-Aida id	14.2
El-Gemeibi	0.4

To obtain stools from school children was relatively simple since discipline is strict and the teachers are very willing to cooperate. If, however, a child was not able to produce a sample no pressure was put upon him to do so and it was collected on a subsequent visit.

For the 3-6 year old children it was necessary to number the houses in the village and approach each one in turn and ask for cooperation. Each child was given a card bearing his name, age, serial number and house number, and he was asked to deliver his sample to the dispensary in the container provided. Older brothers and sisters were asked to help whenever possible and on arrival with the stools the children were rewarded with sweets. Those unable to produce a sample were also rewarded so as to minimise the production of borrowed or animal stools in order to obtain the reward. Without the sweet system the response was very poor and the success of collection depended very much upon it.

Three slides with 25 mg of stool were examined for each stool specimen. If that sample was negative another three slides were examined from a subsequent day's stool and this procedure was repeated on a third day before a child was considered negative. For re-assessment after every 6 months only one stool was taken on account of the work involved. But in the final assessment three stools will again be examined to identify negatives.

The assessment of the 3-6 year old children began six months after that of the school children and it is considered too early as yet to place any significance on the results collected so far. The results of the remaining tables therefore involve the school children only 21 months after the beginning of the assessment period.

Table 3 shows a difference in the incidence rates of about 10% between the treated and non-treated areas. This does not appear significant. However, when the number of conversions (— to +)

TABLE 3. Incidence of *Schistosoma mansoni* infection in Gezira school children 21 months after being identified as negative.

School	No. negative originally	No. examined after 21 months	No. positive	Incidence %
Treated area:				
Bint El Hag	16	14	3	21.43
Azrag	19	17	5	29.41
Sereiha Boys	33	28	7	25.00
Sereiha Girls	38	35	4	11.43
Aidaid Boys	15	12	3	25.00
Aidaid Girls	14	10	3	30.00
Gemeibi	40	34	6	17.65
Totals	175	150	31	20.66
Untreated area:				
Wad Sulfab Boys	28	25	7	28.00
Wad Sulfab Girls	31	20	4	20.00
Kashamir	40	37	15	40.54
Totals	99	82	26	31.70

and reversions (+ to —) are considered (Table 4), a trend towards a reduction in prevalence in the treated area is evident. This must be held in light of the fact that

there was a higher prevalence rate in the treatment area originally. The trend in the non-treated area is for a rise in prevalence.

TABLE 4. Prevalence of *Schistosoma mansoni* in Gezira school children before and 21 months after the beginning of assessment.

Area	No. examined in 1973 and re-examined in 1975	Positive 1973		Conversion -- → +	Reversion + → --	Positive 1975	
		No.	%			No.	%
Treated	588	420	71.43	46	68	398	67.68
Non-treated	296	187	63.18	34	25	196	66.22

Table 5 presents the findings on re-examination of those children that were positive at the outset of assessment. Once again the trend is for a reduction in the intensity of infection in the treated area

compared with the area where no molluscicide has been applied, except for one village (Aidaid) which shows an increase in intensity of infection as measured by egg load.

TABLE 5. Intensity of infection with *Schistosoma mansoni* in Gezira school children initially, and 21 months after the beginning of the assessment.

Village	No. re-examined	Mean egg count in g/head	
		initially	after 21 months
Treated area:			
Gemeibi	118	1308	508
Bint El Hag	83	664	580
Azrag	114	244	140
Sereiha Boys	72	260	196
Sereiha Girls	48	112	60
Aidaid Boys	100	524	672
Aidaid Girls	84	364	552
Totals	619	496	388
Untreated area:			
Wad Sulfab Boys	89	728	424
Wad Sulfab Girls	50	340	468
Kashamir	95	152	528
Totals	184	408	472

Summary

Preliminary assessment of the molluscicide control measures in the Gezira irrigated area in the Sudan by a thick smear stool examination technique indicates that after only 21 months in a

longitudinal study there was reduction in prevalence where chemical has been applied to the canals. Intensity of infection, measured by egg loads has also dropped in the treated area, while in the non-treated area prevalence and intensity of infection are rising.

FOCAL TRANSMISSION OF *SCHISTOSOMA HAEMATOBIMUM* IN LAKE VOLTA, GHANA

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It has been reported by Odei (1973) that *Bulinus truncatus rohlfsi*, the intermediate host of *Schistosoma haematobium* in the Volta area of Ghana, is widely distributed in Lake Volta. A WHO/UNDP schistosomiasis project was established at the lake in 1971 and the preliminary work was started in 1972. Findings showed that snails were distributed along the shore and that snails collected at depths of 1-3 metres were mainly associated with the aquatic weed, *Ceratophyllum* (Chu & Vanderburg, unpublished data; Odei, 1973).

Paperna (1967, 4th Report) classified the lake shore into undisturbed unpopulated areas and disturbed areas populated by fisherfolk. He reported in the same document that infected snails were found in the latter area, but rarely in the former area. Observations in the present project at lake-side villages showed that human activities are mainly limited to «water contact sites» (WCSs) which are formed as a result of the villagers' need for easy accessibility to the lake shore and for boating outlets into the deeper water. Preliminary sampling showed that infected snails were almost entirely confined to these WCSs; they were not normally found in the areas between WCSs (Vanderburg & Chu, unpublished).

27 months of ecological studies on *B. rohlfsi* in WCSs carried out by Klumpp

& Chu (unpublished) revealed that transmission is low during the phase of rapid lake rise from August through October and relatively high during the phase of water regression from November through July. Because of constant fluctuation in the lake level, WCSs change every month. The first half of each annual lake decline (November through March) has been the main transmission season, when most of the transmission occurs in pocket-shaped WCSs. Hence, it was desirable to additionally study the distribution of infected lake snails within pocket-shaped WCSs.

Materials and Methods

The prevalence of urinary schistosomiasis at Akotui West village has averaged over 90%. In the present study, 5 WCSs were chosen for regular snail sampling by using the palm-mat method of sampling (Vanderburg & Chu; Klumpp & Chu, unpubl. data). In the main WCS, 42 mats were placed systematically in the water every month for 27 continuous months from March 1973 through May 1975. This WCS is comparatively large with an average surface area of approximately 400 m², pocket-like in shape during most months except at very low water level. *Ceratophyllum* is usually present, sometimes scattered and sometimes dense, in zones mostly 5-15 m away from the shoreline.

The 4 other WCSs selected were combined as a group. They were smaller in size and had less human activity. From December 1974 through February 1975, these WCSs were also mainly pocket-like; they were sampled 8 times at an average interval of 10 days. In each habitat, 10 mats were placed in the water in pairs, 1-2 m apart, at 1, 3, 5, 7, and 9 m away from the curvature of the shoreline. All mats were left in the water for 2 days. After snails were picked-up from the mats at the end of the exposure period, a hand search was additionally carried out in the off-shore zone beyond the 9 metre line. Snails collected were brought back to the laboratory for crushing and were examined under a dissecting microscope for evidence of schistosome infection. Those which contained mature schistosome cercariae were considered positive for infection.

Results

The densities of *B. rohlfsi* and mature cercarial infection per palm mat per month, by sampling rows and according to distance from the shore in the main

WCS (site II) at Akotui West over the 27-month period, are presented in Fig. 1. The densities of snails and infected snails in the 4 secondary WCSs (A, B, C, D), according to distance from the shore, are shown in Table 1.

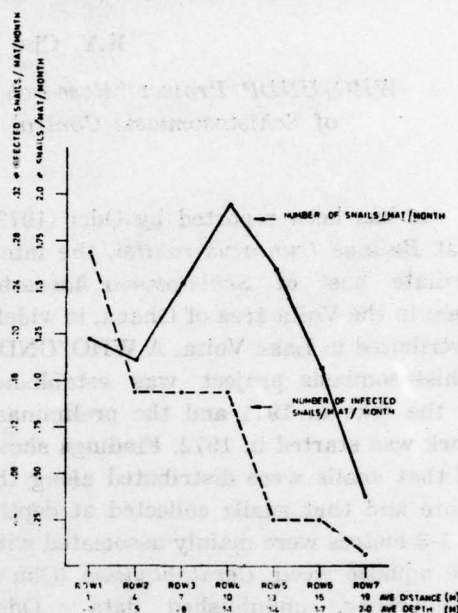


Fig. 1. Densities of *Bulinus rohlfsi* and mature cercarial infections per palm leaf trap at main water contact site (II), at Akotui West, March-May 1975.

TABLE 1. Distribution of infected *Bulinus rohlfsi* among snails collected in 4 pockets (A,B,C,D) on the shore of Lake Volta, in 8 samplings by 10 (2×5) palm-leaf mats.

Distance from the shore (metres)	Water contact site				Total	% of infection	Potential population of transmission
	A	B	C	D			
1	3/12	10/47	0/16	0/6	13/81	16.0	72.2
3	0/17	0/42	2/4	0/5	2/68	2.9	11.1
5	2/2	0/14	0/3	0	2/19	10.5	11.1
7	0/2	1/12	0/3	0/3	1/20	5.0	5.6
9	0/9	0/15	0/13	0/4	0/41	0	0

The graph shows that the density of infected snails was highest near the shoreline, fell to approximately one-half in the zone 4-10 m from the shore, was further reduced to 1/7th in the zone 10-16 m from the shore, and to only 6% of its value in the zone 16-20 m from shore. The same figure shows that the highest snail density occurred in the zone 7-14 m from the shoreline, where *Ceratophyllum* is normally abundant on the lake bottom.

Table 1 supports the above finding that infected snails in the lake occur mostly very close to shore and rarely in off-shore areas. The summated result of 8 collections in the 4 pocket-shaped WCSs within the 3 months sampling period showed that the number of infected snails collected was 13, 2, 2, 1, and 0 at 1, 3, 5, 7, and 9 m respectively away from the shoreline. Whenever snails were collected beyond a distance of 9 m from shore by hand, they were negative for schistosome infection. These findings indicate that transmission is focal and that intensity of infection is high near the shoreline and low away from the shoreline.

Discussion

Paperna (1967) reported that transmission of urinary schistosomiasis in the lake occurs in disturbed populated areas. Vanderburg & Chu (unpubl.) found that in such disturbed populated areas, infected snails were collected only in WCSs. The results of the present paper point out that even within a WCS, lake transmission is further localized, with infected snails concentrated very near the shoreline. Thus, transmission in the Volta Lake is essentially focal.

The reasons for an abundance of infected snails near the shore are multiple. First, this zone is shallow and is an im-

portant place of human activity; miracidial concentration also is therefore usually high. Secondly, although children may swim a little further off-shore and miracidia from these children disperse radially, those toward the open lake are lost, whereas miracidia heading toward the shore may then swim around the shoreline limit. In the latter case, the shoreline may create a rebounding barrier to miracidia so that the chance for snail-miracidial contact increases. This phenomenon can be demonstrated in a Petri-dish in which miracidia usually move around the rim. It is already known (Vanderburg & Chu, unpubl.) that miracidial infection of snails in the lake usually takes place on or near the bottom. Those miracidia which wander off the shore have little chance to infect snails.

The rebounding factor may be one of the reasons for the higher infection rates of snails living near the lake shoreline. Living or dead plants and animals (including man and fishes) may enhance this rebounding effect on the miracidia. *Ceratophyllum*, an aquatic weed abundant in Lake Volta, is found to have a close association with snails and its dense growth acts as a good rebounding surface. Because of the vinelike stems of this plant, the miracidia inside this intricate mass of vegetation seem to become trapped in close proximity to the snails residing in them; the infection rates of the vector snail in a *Ceratophyllum* mass is therefore usually high, with distribution of snail infection patchy. Recently, Dr. Jobin (personal communication) proposed the use of decoy animals in Lake Volta, especially of ampullariid snails, to reduce the chances of contact between the vector snails and schistosome miracidia. However, unless the decoy snails are a susceptible target for the schistosome miracidia, the miracidial concentration will not

become reduced, because the decoy snails will act as further rebounding matter. As a result, transmission would then not become reduced to an acceptable level. Recently, Upatham & Sturrock (1973) made field investigations on the effect of other aquatic animals on the infection of *Biomphalaria glabrata* by *Schistosoma mansoni* miracidia and concluded that in St. Lucia it seems unlikely that decoy

animals prevent natural *S. mansoni* transmission although they may limit its severity.

It is now known that transmission of urinary schistosomiasis in Lake Volta is both seasonal and focal, and interruption of transmission can be achieved by focal treatment through focal mollusciciding and weed clearance.

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**STUDIES ON THE INTENSITY OF *SCHISTOSOMA JAPONICUM*
INFECTION IN LINDU VALLEY, CENTRAL
SULAWESI (CELEBES), INDONESIA**

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Although the first autochthonous infection of *Schistosoma japonicum* in Central Sulawesi (Celebes), Indonesia, was discovered by Brug & Tesch as early as 1937, intensified studies on the epidemiology of the disease and the ecology of the intermediate host were only carried out after the discovery of *Oncomelania hupensis lindoensis* (Hadidjaja et al., 1972). Since 1971 prevalence surveys were conducted, covering from a limited group of individuals to the entire village population of Lindu Valley (Hadidjaja et al., 1972 ; Clarke et al., 1974).

An initial attempt to quantitate the number of eggs in stool samples of positive cases was made in 1974. Forty-nine persons belonging to the 15-30 year age group were examined and found to have a mean egg load of 46,230 eggs per 100 grams of stool sample, using the Stoll method (Kurniawan et al., 1975).

This study is part of an overall investigation to collect base-line information on the intensity of infection based on quantitative egg counts among the entire population of Anca and Langko villages prior to the implementation of a schistosomiasis control programme. It was conducted in January 1975.

Materials and Methods

First, all houses in the 2 villages of Anca and Langko were numbered systematically and all the inhabitants were listed. The census comprised 391 and 464 individuals in Anca and Langko, respectively.

People were requested to submit to examination. Stool containers were distributed in the evening and collected with specimens the following morning.

Each stool was processed using the modified Kato technique (Katz et al., 1973) in the following manner : A piece of wire screen with about 160 meshes per square inch was placed on top of the sample and pressed gently to allow the faecal material to be strained. With the use of an applicator stick the strained material was transferred to a faecal measuring device made of a rectangular piece of cardboard (2 mm thick) with a hole measuring 5.5 mm in diameter punched in the centre. When the hole was filled and levelled, the cardboard was removed, leaving the faecal material on the glass slide. Cellophane tape measuring 2 × 4 cm, soaked for 24 hr in malachite green solution (Martin & Beaver, 1968), was

placed over the faecal material. In order to facilitate easier detection of eggs, the smear was thinned out evenly by means of another glass slide. Slide preparations were set aside for 30 min before examination.

Two slides were prepared from each stool sample, each being examined by a different person. The average number of eggs/slide was taken from the 2 slides.

For evaluation purposes the results were expressed in terms of number of eggs/gram sample (epg).

To determine the number of eggs/gram sample per positive case, 100 stool samples from the inhabitants were weighed before covering them with cellophane tape and the mean weight in milligrams was calculated. The mean weight was then used in the following formula :

$$\frac{1000}{\text{mean weight of 100 samples}} (= \text{FACTOR}) \times \text{average egg count per slide per positive case} = \text{number of eggs/gram per sample per positive case}$$

Only 347 out of 391 individuals from Anca and 391 out of 464 persons from Langko completed the examination.

Persons with negative specimens were requested to submit a second and then a third sample, if still found free of *S. japonicum* eggs. Hence an individual was considered to be negative only after 3 successive stool examinations showed the absence of eggs.

Results

A total of 465 persons were found to be positive for *S. japonicum* eggs (245 from Anca and 220 from Langko). Of this number 68.38% were found positive during the first examination. The figures for the second and third examinations were 20.00%, 11.62% respectively (Table 1).

TABLE 1. Results of 3 consecutive stool examinations for positive cases of *Schistosoma japonicum* infection (January 1975).

Village	Positive	Examination			Total
		1st	2nd	3rd	
Anca	Nos.	181	34	30	245
	%	73.88	13.88	12.24	100
Langko	Nos.	137	59	24	220
	%	62.27	26.82	10.91	100
Total	Nos.	318	93	54	465
	%	68.38	20.00	11.62	100

Table 2 shows the population coverage and prevalence rates of infection in both Anca and Langko villages. Percentage coverage for the 2 villages was

88.75% and 84.27%. Only persons with complete examinations were included, i.e., 3 examinations for negative individuals and 1, 2 or 3 examination for positive

cases. Accordingly the figures for coverage were relatively low, as individuals with 1 or 2 negative examinations were not counted.

The prevalence rate of *S. japonicum* infection obtained in Anca was 70.61%, for Langko 56.27%. Prevalence of the disease, arranged according to age-groups and sex, is given in Tables 3 and 4.

The mean number of eggs per gram of faeces was 112.34 for Anca and 99.70 for Langko. Tables 5 and 6 show the intensity of the infection, arranged according to age and sex for the 2 areas.

Figures 1 and 2 give a graphic representation of prevalence and intensity of infection according to age groups.

TABLE 2. Prevalence rates of *Schistosoma japonicum* infection in Anca and Langko villages, Lindu Valley Central Sulawesi (January 1975).

Village	Total Population	No. examined	% covered	No. positive	Prevalence rate %
Anca	391	347	88.75	245	70.61
Langko	464	391	84.27	220	56.27

TABLE 3. *Schistosoma japonicum* infection according to age and sex in Anca village, Lindu Valley, Central Sulawesi (January 1975).

Age group (years)	Males			Females			Total		
	No. exam.	No. pos.	Prev. rate	No. exam.	No. pos.	Prev. rate	No. exam.	No. pos.	Prev. rate
0 — 4	24	10	41.6%	14	2	14.2%	38	12	31.5%
5 — 9	33	21	63.6%	27	16	59.2%	60	37	61.6%
10 — 14	31	26	83.8%	24	15	62.5%	55	41	74.5%
15 — 19	15	12	80.0%	18	14	77.7%	33	26	78.7%
20 — 24	6	4	66.6%	19	13	68.4%	25	17	68.0%
25 — 29	13	11	84.6%	6	6	100.0%	19	17	89.4%
30 — 34	8	8	100.0%	13	12	92.3%	21	20	95.2%
35 — 39	12	12	100.0%	13	9	69.2%	25	21	84.0%
40 — 44	7	6	85.7%	6	5	83.3%	13	11	84.6%
45 — 49	7	7	100.0%	11	9	81.8%	18	16	88.8%
50 — 54	10	8	80.0%	5	2	40.0%	15	10	66.6%
55 — 59	1	0	0.0%	5	3	60.0%	6	3	50.0%
60 — 64	0	0	0.0%	7	3	42.8%	7	3	42.8%
65 +	3	3	100.0%	9	8	88.8%	12	11	91.6%
Total . . .	170	128	75.2%	177	117	66.1%	347	245	70.6%

TABLE 4. *Schistosoma japonicum* infection according to age and sex in Langko village, Lindu Valley, Central Sulawesi (January 1975).

Age group (years)	Males			Females			Total		
	No. exam.	No. pos.	Prev. rate	No. exam.	No. pos.	Prev. rate	No. exam.	No. pos.	Prev. rate
0 — 4	23	6	26.0%	29	3	10.3%	52	9	17.3%
5 — 9	34	16	47.0%	28	12	42.8%	62	28	45.1%
10 — 14	23	18	78.2%	32	19	59.3%	55	37	67.2%
15 — 19	11	8	72.7%	14	6	42.8%	25	14	56.0%
20 — 24	12	6	50.0%	18	11	61.1%	30	17	56.6%
25 — 29	12	11	91.6%	19	13	68.4%	31	24	77.4%
30 — 34	12	8	66.6%	8	5	62.5%	20	13	65.0%
35 — 39	9	8	88.8%	10	4	40.0%	19	12	63.1%
40 — 44	13	12	92.3%	12	8	66.6%	25	20	80.0%
45 — 49	14	9	64.2%	9	7	77.7%	23	16	69.5%
50 — 54	12	9	75.0%	10	6	60.0%	22	15	68.1%
55 — 59	4	2	50.0%	2	1	50.0%	6	3	50.0%
60 — 64	3	3	100.0%	4	4	100.0%	7	7	100.0%
65 +	5	2	40.0%	8	3	37.5%	13	5	38.4%
Total . . .	187	116	62.0%	204	104	50.9%	391	220	56.2%

TABLE 5. Intensity of *Schistosoma japonicum* infection expressed in mean number of eggs per gram of stool sample arranged according to age and sex among positive cases in Anca village, Lindu Valley, Central Sulawesi (January 1975)

Age group (years)	Males		Females		Total	
	No. (+)	Mean eggs/g	No. (+)	Mean eggs/g	No. (+)	Mean eggs/g
0 — 4	10	39.90	2	15.75	12	35.87
5 — 9	21	84.50	16	108.28	37	94.78
10 — 14	26	99.75	15	246.40	41	153.40
15 — 19	12	76.12	14	67.50	26	71.48
20 — 24	4	34.12	13	234.23	17	187.14
25 — 29	11	151.77	6	178.50	17	161.20
30 — 34	8	103.68	12	132.12	20	120.75
35 — 39	12	101.50	9	147.00	21	121.00
40 — 44	6	105.00	5	121.80	11	112.63
45 — 49	7	45.00	9	79.33	16	64.31
50 — 54	8	31.50	2	57.75	10	36.75
55 — 59	0	0	3	87.50	3	87.50
60 — 64	0	0	3	276.50	3	276.50
65 +	3	24.50	8	101.06	11	80.18
Total mean	128	84.41	117	143.32	245	112.54

TABLE 6. Intensity of *Schistosoma japonicum* infection expressed in mean number of eggs per gram of stool sample arranged according to age and sex among positive cases in Langko village, Lindu Valley, Central Sulawesi (January 1975).

Age group (years)	Males		Females		Total	
	No. (+)	Mean eggs/g	No. (+)	Mean eggs/g	No. (+)	Mean eggs/g
0 — 4	6	29.75	3	24.50	9	28.00
5 — 9	16	70.87	12	40.25	28	57.75
10 — 14	18	56.58	19	144.78	37	101.87
15 — 19	8	116.81	6	106.75	14	112.50
20 — 24	6	239.75	11	35.31	17	107.47
25 — 29	11	92.59	13	62.19	24	76.12
30 — 34	8	246.75	5	75.60	13	180.92
35 — 39	8	207.37	4	26.25	12	147.00
40 — 44	12	79.62	8	280.87	20	160.12
45 — 49	9	99.16	7	61.50	16	82.68
50 — 54	9	59.50	6	152.25	15	96.60
55 — 59	2	21.00	1	199.50	3	80.50
60 — 64	3	84.00	4	42.00	7	60.00
65 +	2	73.50	3	56.00	5	63.00
Total mean	118	103.22	102	95.63	220	99.70

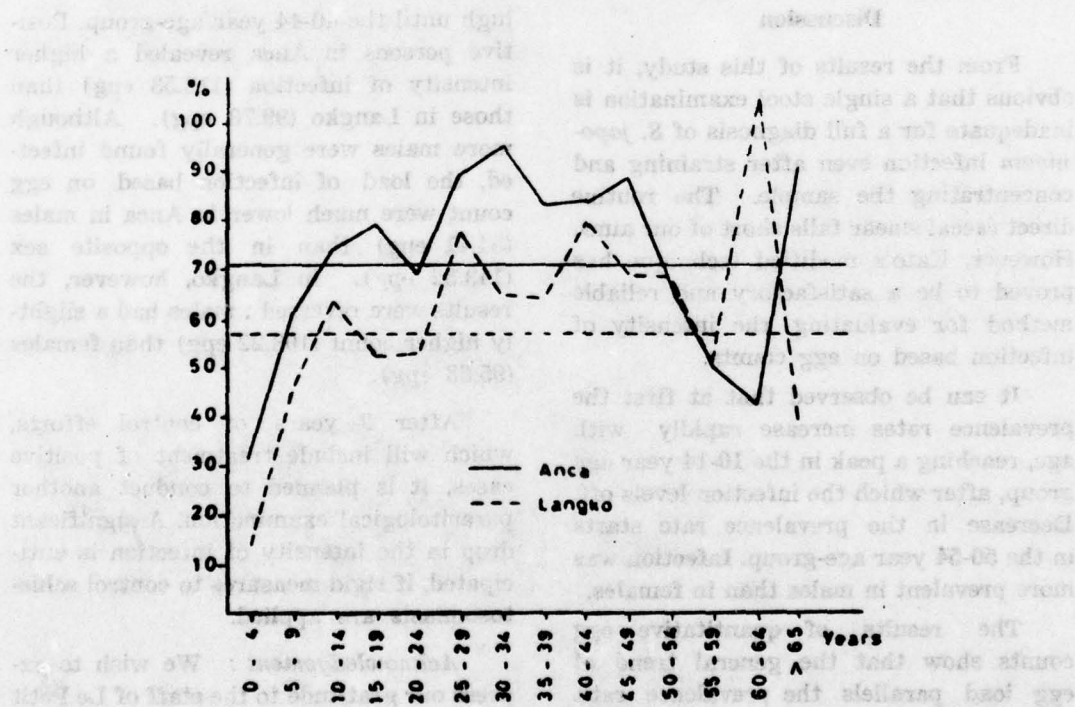


Fig. 1. Prevalence rates of infection among the village population of Anca and Langko according to age groups (January 1975).

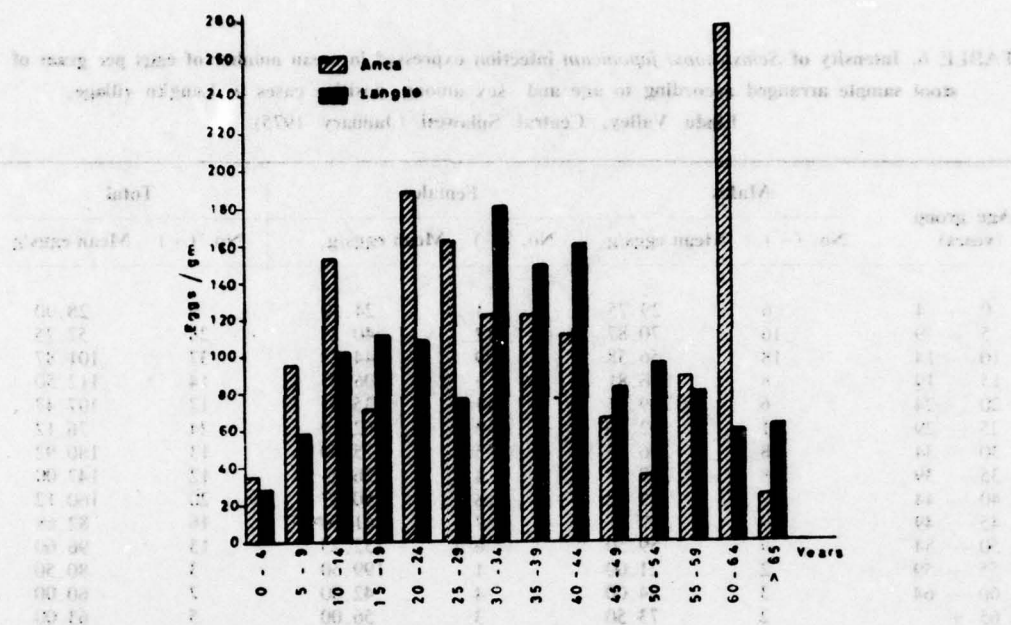


Fig. 2. Intensity of infection based on quantitative egg counts taken from positive cases in Anca and Langko according to age groups (January 1975).

Discussion

From the results of this study, it is obvious that a single stool examination is inadequate for a full diagnosis of *S. japonicum* infection even after straining and concentrating the sample. The routine direct faecal smear falls short of our aims. However, Kato's modified technique has proved to be a satisfactory and reliable method for evaluating the intensity of infection based on egg counts.

It can be observed that at first the prevalence rates increase rapidly with age, reaching a peak in the 10-14 year age group, after which the infection levels off. Decrease in the prevalence rate starts in the 50-54 year age-group. Infection was more prevalent in males than in females.

The results of quantitative egg counts show that the general trend of egg load parallels the prevalence rate. There is a rapid increase of egg counts with increase in age reaching a peak at the 10-14 year age-group, and remaining

high until the 40-44 year age-group. Positive persons in Anca revealed a higher intensity of infection (112.53 epg) than those in Langko (99.70 epg). Although more males were generally found infected, the load of infection based on egg count were much lower in Anca in males (84.41 epg) than in the opposite sex (143.32 epg). In Langko, however, the results were reversed: males had a slightly higher count (103.22 epg) than females (95.63 epg).

After 2 years of control efforts, which will include treatment of positive cases, it is planned to conduct another parasitological examination. A significant drop in the intensity of infection is anticipated, if rigid measures to control schistosomiasis are applied.

Acknowledgement: We wish to express our gratitude to the staff of Le Petit Soleil laboratory. Without their help and assistance, this study would not have been possible.

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EPIDEMIOLOGY AND PROPOSED CONTROL OF SCHISTOSOMIASIS IN SOUTHERN LAOS

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Human schistosomiasis has been reported in recent years from a number of countries of Southeast Asia, including Thailand, Laos, Cambodia, Malaysia and Indonesia.

The first case of Southeast Asian origin was reported in 1957 by Vic-Dupont et al. in a Paris hospital. In 1959, Chaiyaporn et al. found human cases in peninsular Thailand. Follow-up studies in Thailand were made of geographic distribution (Harinasuta & Kruatrachue, 1960, 1964), pathogenicity and diagnosis (Harinasuta et al., 1967), and animal reservoirs (Kruatrachue et al., 1964), but transmitting snails were not found. Isolated and still mysterious cases were also reported in Northern and Northeast Thailand (Lee et al., 1966 ; Desowitz et al., 1967).

Attention was soon focused on Southern Laos, where acute and chronic human cases were found on Khong Island in the Mekong River (Iijima et al., 1971 ; Sornmani et al., 1971). Cases in humans were also found in Cambodia in 1968 (Audebaud et al.), all apparently centered in the provincial capital of Kratié.

Because of the unsettled state of the country, the site at Kratié cannot be visited. However, there is little reason to doubt that the Laotian and Cambodian

parasites represent closely related strains, and the few cases that have been identified in Northeast Thailand (Desowitz et al., 1967) probably belong with this group. The cases from Nakhon Si Thammarat in peninsular Thailand still present a problem (field studies in recent years have been interrupted by security difficulties) ; studies of egg morphology, however, support the idea that these parasites may be more closely related to the Mekong *Schistosoma* than to other Asian geographic strains of *S. japonicum* (Sornmani, 1969). The single human case reported from Northern Thailand by Lee et al. (1966) was pathologically and geographically aberrant and cannot be discussed here.

A single case of autochthonous schistosomiasis has been reported from West Malaysia (Murugasu & Por, 1973). In the absence of follow-up studies, this case represents an anomaly and will also not be discussed.

In Indonesia, transmission is known only from the Lindu and Napu valleys of Central Sulawesi (Oemijati, 1969 ; Carney et al., 1974). The parasite is *S. japonicum* and the transmitting snail in the Lindu valley has been described as a subspecies of *Oncomelania hupensis* (Davis & Carney, 1973). The range of this parasite seems to represent a geographic

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extension from the Philippines; it is probably unrelated to the Mekong *Schistosoma*.

Background of the Situation in Laos

The initial warnings of Vic-Dupont et al. (1957) and of Barbier (1966) directed the attention of the World Health Organization toward the problem posed by the discovery of human schistosomiasis in Laos. A number of short-term expeditions were sent out by the Western Pacific Regional Office, at first to search for cases in the larger centers of population (Ito & Jatanasen, 1961; Zeville & Santos, 1961), and eventually to Khong Island, in the Mekong River near the Lao-Khmer border, where human cases were detected (Iijima & Garcia, 1967; Iijima et al., 1971, 1973) and suspect snails were studied (Lo et al., 1971).

Somewhat earlier, Brandt (1970) had reported failure to prove any known snail as being able to transmit schistosomiasis at Khong (see below).

At the request of the Committee for Coordination of Investigations of the Lower Mekong Basin (Mekong Committee), a field team was sent to Southeast Asia in 1970 by the Office of Environmental Sciences of the Smithsonian Institution with the aim of finding a transmitting snail in the Lower Mekong Basin. The team had supporting assistance from the United States Agency for International Development through its Office of Regional Economic Development (RED). In cooperation with the Faculty of Tropical Medicine, Mahidol University, Bangkok, and the National Public Health Laboratory, Vientiane, Laos, the team was able to identify a transmitting snail, study its aquatic ecology and geographic distribution, complete the life cycle of the Mekong *Schistosoma* in the laboratory,

and study details of epidemiology on Khong Island (Smithsonian Institution, 1974).

The Geography and Population of Khong Island

The population of Laos is thought to approximate 3 million. Half of the people are said to inhabit riverine sites, mostly on or near the Mekong River, with an average population density approaching 70/km² (Pathammavong, 1972).

Khong Island, in Sithandone Province bordering Cambodia in the south, has the following coordinates: 14° 05-14' N latitude by 105° 47-52' E longitude. The island is one of the largest in the Mekong River, approximately 8 by 12 km at its widest and longest with a consequent area of 96 km² (37 mi.²). The central third of Khong Island is dominated by 2 elevations of, respectively, 239 and 230 m and is covered with scrubby dipterocarp forest and dry evergreen forest. The southern third of the island is flat and overspread with paddy fields. The northern third has a sparser population and the paddy fields are interspersed with forested areas.

The largest center of population is the provincial capital, Khong Town, located on the southeast shore of the island, with a population of slightly less than 1,000. The total population of Khong Island has been estimated from 1967-68 census figures to be less than 3,000 (Sornmani et al., 1971). Considering the area of Khong Island, it will be noted that this figure is less than half of the density estimated above for Lao riverine populations in general although most of the people on Khong live at the river's edge.

The Mekong River at Khong Island has an annual vertical movement of about

10 m. A seasonal peak in water level occurs in September; lowest levels are usually measured in April or May. The river is not known to escape from its channel during high water periods at Khong and flooding has not been reported.

The banks of the island tend to be steep, leading down to a river bed characterized by the presence of gravel and stones but there are many areas of sandy shore with more gradual slope, particularly toward the north end of the island.

Prevalence and Distribution in Laos

Vientiane. A survey conducted in Vientiane under the auspices of WHO (Iijima et al., 1973) revealed the presence of individuals, mostly school children, who gave positive reactions to the skin test but were parasitologically negative (Table 1). No reasons can be adduced for the positive reactions. In an unrelated study of intestinal parasites in Vientiane, 2,493 stool specimens from individuals of all ages, both sexes, and from all parts of town failed to show schistosomes when direct smears were examined, although the investigators were trained to recognize the eggs of the Mekong *Schistosoma* had these been encountered (Sornmani et al., 1974).

Paksé. In Paksé, Ito and Jatanasen (1961) found only two positive and 12 doubtful skin tests in 802 subjects, and none were positive for schistosome eggs. Iijima et al., (1973) examined 1,478 persons, mostly school children, and found that 200 were skin-test positive and 20 were skin-test doubtful. Of 203 children examined parasitologically, three were passing eggs of *Schistosoma*; however, these were lycée students who had come from Khong Island (which does not have a lycée) and the likelihood that they represented intro-

duced cases was very strong. In this connection, it should be pointed out that although people move easily and frequently between Paksé and Khong, yet schistosomiasis has evidently not become implanted at Paksé.

Khong. The first of the WHO investigations at Khong Island was conducted by Iijima & García (1967) (see also Iijima et al., 1973). Again, subjects included primary school children and some adults. Of 360 skin tests in Khong Town, 88 (24.4%) were positive and 182 (50.6%) were doubtful; 136 stools were examined by direct smear, using 2 to 5 smears and there were 36 positives (26.5%). In other villages of Khong Island, 652 persons were skin-tested and 98 (15%) were positive; 411 stools were examined and 11 (2.7%) contained eggs.

In 1968-69, the same investigators repeated their work at Khong Island and its immediate environs (Iijima, 1970; Iijima et al., 1973). Skin test results in the follow-up study differed markedly from those of the earlier study, suggesting that different criteria had been employed for reading them; 178 of 223 individuals (79.8%), mostly primary school children, gave positive skin tests. Results of stool examinations were in close agreement with the previous study: there were 49 positives in 149 (32.9%).

A study by Sornmani and colleagues in 1969 (Sornmani et al., 1971) produced skin test results consistent with those of the WHO's first (1966-67) study; of 456 tests there were 136 positives (29.8%) and 160 doubtfuls (35.1%). The stool examinations, utilizing a concentration technique, gave results not dissimilar from previous studies: in Khong Town, 27 of 118 stools were positive (22.9%) and 3 of 91 stools from elsewhere on Khong Island were positive (3.3%).

TABLE 1. Summary of recent epidemiological surveys for schistosomiasis in Laos.

LOCATION	Date Survey Done	SKIN TEST				STOOL EXAMINATION				References
		No. Tested	No. Positive	%	No. Doubtful	%	No. Exam.	No. Positive	%	Method*
VENTIANE	1968-69	935	154	16.5	20	2.1	121	0	0.0	D.S.
	1960	802	2	0.2	12	1.5	158	0	0.0	D.S.
PAKSE	1968-69	1,478	200	13.5	20	1.4	203	3	1.5	D.S.
	1966-67	360	88	24.4	182	50.6	136	36	26.5	D.S.
KHONG ISLAND Khong Town & Hat Sai Khun	1968-69	223	178	79.8	4	1.8	149	49	32.9	D.S.
	1969	456	136	29.8	160	35.1	118	27	22.9	F.E.C.
Elsewhere on Khong Island	1966-67	652	98	15.0	137	21.0	411	11	2.7	D.S.
	1969	415	113	27.2	117	28.2	91	3	3.3	F.E.C.

* D.S. = direct smear; F.E.C. = formalin-ether concentration.

In all 3 studies, single stool specimens were taken for examination, usually from skin-test positives. It is likely that repeated examinations would have produced somewhat higher rates, at least in the children. It appears, however, that adults do not pass many eggs; Sornmani et al. (1971) reported that only 30 of 209 individuals with positive and doubtful skin tests could be demonstrated to be passing eggs, and none of these was over 30 years of age.

Two main facts emerge from these studies: (1) Although skin testing is useful as a preliminary screen technique, the interpretation of results can vary considerably in the same group at different times, even in the hands of the same investigators; (2) there was much similarity between the prevalence data based on stool examinations in the three different studies (in which, of course, many samples may have been duplicated): infection rates ranged from 22.9 to 32.9% with an average of 27.8% in Khong Town and Ban Hat Sai Khun (directly across the river). The average was reduced to 13.9% when all age groups on Khong Island were included. In Khong Town, the prevalence in primary and secondary school children was higher than the overall average, in the range of 30-40%.

The initial impressions of the first workers that Mekong schistosomiasis was milder than elsewhere in Asia has now been considerably modified. Cases of severe debilitation in association with hepatic fibrosis and ascites have been seen on Khong Island and deaths attributed to schistosomiasis have been recorded. It is evident that Mekong schistosomiasis is to be feared as much as any other geographic form of the Asian disease.

Transmission on Khong Island

Early reports (Vic-Dupont et al., 1957; Barbier, 1966) based on systematic examination of expatriate patients and their origins focused attention on Khong Island, where relatively large numbers of active cases were ultimately detected (Iijima & Garcia, 1967; Sornmani et al., 1971; Iijima et al., 1973).

A common denominator in all the human cases was their association with Khong Town, the major center of population on Khong as well as the provincial capital. More specifically, there was always a history of swimming in the Mekong River somewhere within the two km stretch of shore between the Ban Xieng Wang section to the north and the Government Hospital compound to the south (Sornmani et al., 1971). Most people bathed at Ban Xieng Wang. Transmission at this site was demonstrated directly, in April, 1972, when sentinel mice exposed in floating cages in shallow water became infected with the Mekong *Schistosoma* (Kitikoon et al., 1973). Mice exposed in the same location a year before had not developed infections. The earlier failure was blamed on exposing the mice in too fast current. The successful exposures may have been associated with the extraordinarily large population of *Lithoglyphopsis aperta* that was observed in the river in April, 1972.

In view of the concentrated population at Ban Xieng Wang, the presence there of easy access to a popular bathing area, safe for children, adjacent to a small peninsula and small, rocky islets (fully exposed only toward the end of the dry season), and the annual presence of large numbers of *L. aperta* snails (see below), the conviction was acquired that this relatively small area of about 100 m² represented a principal, or the main,

transmission site on Khong Island (Kitikoon et al., 1973). However, insufficient time has been spent in experimentally excluding other sites around the shore of Khong Island (or on the mainland) as actual or potential transmission sites.

Malacology

Harinasuta et al. (1972) demonstrated that an aquatic hydrobiid snail, *Lithoglyphopsis aperta* Temcharoen, 1971, was experimentally capable of transmitting the parasite. The genus belongs in the Subfamily Triculinae (Davis et al., 1976). This small (about 3 mm long) snail has been found only in a 250 mile section of the lower Mekong River and in one of its tributaries. The species has been reported from Sompamit Falls, Khong Island, and Champassak, Laos (Temcharoen, 1971), and we have collected specimens at Khong Chiam (Ban Dan) at the mouth of the Mun River, and in the Mekong at Khemmarat, Thailand (Smithsonian Institution, 1974). A morphological variant is found in the Mun River of Northeast Thailand (see below).

In the Mekong, snails are collected in small numbers in the early part of the dry season and in increasingly large numbers as the water level drops. The largest numbers of mature snails have been taken in May or early June.

They are entirely aquatic and are found in shallow (40-50 mm) to moderately deep (0.5-2.0 m) water on solid surfaces such as stones, twigs, beer cans, clam shells, leaves, etc., in the presence of a detectable current, high oxygen tension, high pH (between 8.0 and 8.5 in daytime) and usually clear water (Sornmani et al., 1973; Davis et al., 1976). At Khong Island such conditions become increasingly available as the river level drops, exposing numbers of rocky islets with dense growths of a euphorbeacean

rheophytic shrub, *Homonoia* sp., off the east shore (Kitikoon et al., 1973).

During April, May and early June, the snails abound on such islets near the main bathing area of Khong Town.

To date, completion of the life cycle of the Mekong *Schistosoma* has been experimentally achieved only in *L. aperta*. Other closely related and sympatric species of Hydrobiidae appear, however, to be attractive to the miracidia and penetration may occur although development of the resulting sporocysts ceases after a few days. Table 2 lists reports of some of the species of Hydrobiidae that have been tested.

Lo et al., (1971) failed to infect five geographic subspecies of *Oncomelania* originating in mainland China, Japan, Philippines and Taiwan with miracidia of the Mekong *Schistosoma*. In the laboratory in Bangkok, miracidia of a Philippine strain of *S. japonicum* penetrated *L. aperta* and formed identifiable sporocysts but the cycle was not completed and cercariae did not emerge.

Among other suspected snails, *Pachydrobia bavayi* stands out. Lo et al., (1971) reported that sporocysts were found shortly after *Pachydrobia bavayi* were penetrated by miracidia of the Mekong *Schistosoma*, as well as by a Japanese strain of *S. japonicum*, although results were negative or uncertain using miracidia of a Formosan and a Philippine strain. Cercariae resulted from none of these attempts. The significance of snails which attract miracidia but which are unsuitable for the completion of the parasitic life cycle will not be lost on epidemiologists. Such snails may occur in large numbers and could, theoretically, reduce miracidial density in exposure areas. We now believe that *Pachydrobia bavayi* is one of these.

TABLE 2. — Susceptibility of hydrobiid snails from the Lower Mekong Basin to Infection with the Mekong *Schistosoma*

Species	Miracidia penetrated snail	Sporocysts developed beyond 24 hr*	Cercariae emerged or matured	References
<i>Hubendickia</i> sp.**	yes	yes***	no	Smithsonian Institution, 1974
<i>Hydrobia</i> sp.	yes	yes	no	Smithsonian Institution, 1974
<i>H. elongata</i> (= <i>H. hospialis</i>)	yes	yes	no	Brandt, 1968
<i>Jullienia hamandi</i>	no	—	—	Brandt, 1974
<i>J. nuda</i>	no	—	—	" "
<i>J. rolfsbrandti</i>	no	—	—	" "
<i>Lithoglyphopsis aperta</i>	yes	yes	yes	Harnasuta <i>et al.</i> , 1972
<i>Mamigiella</i> sp.	yes	yes	no	Smithsonian Institution, 1974
<i>M. conica</i>	yes	yes	not	(unpublished data)
<i>M. expansa</i>	yes	NR	no	Brandt, 1974
<i>Pachytrabia barayi</i>	yes	yes	no	Lo <i>et al.</i> , 1971
<i>P. crooki</i>	yes	no	no	Smithsonian Institution, 1974
<i>Paraprososthenia lewyi</i>	no	—	—	Brandt & Tencharoen, 1971

* NR = not reported

** Brandt (1974) states: "Species of this genus are not accepted by miracidia of *Schistosoma japonicum* from the Mekong valley."

*** Poorly fixed specimens, difficult to read.

† Sporocysts developed to the secondary (daughter) stage.

Races of *L. aperta*: Three morphologically distinct forms of *L. aperta* have been found in the Mekong and Mun rivers. They are thought to represent races of *L. aperta* and have been given the identifying tags alpha, beta, and gamma (Davis et al., 1976). The differences are based on length and width of shell and aperture, pigment distribution on the mantle, and, at least in preliminary experiments, susceptibility to infection with the Mekong *Schistosoma*. The alpha and gamma races are sympatric in the Mekong River near Khemmarat but, in fact, only mature alpha and immature gamma have been found together. Gamma race snails are the «tiger-stripe» forms first identified as transmitters at Khong Island, where they are dominant during April and May. A very old shell of alpha race was figured by Temcharoen (1971) as the type of the species. The beta race has been collected only in the Mun River of Thailand.

The species *aperta* was apparently wrongly placed in the genus *Lithoglyphopsis* on the basis of a misidentified radula. However, at present, there is no other genus to which the species can be assigned. Too few data are available for the numerous related species in the Mekong and elsewhere to permit creation of a new genus (Davis et al., 1976).

Reservoir Hosts

Dogs : Several investigators have incriminated dogs as carriers of the Mekong *Schistosoma*. Dogs in Khong Town often join people who are bathing in the shallow water of the infection site. From personal experience it is possible to assert that they also defecate with some regularity among shrubs on wet mud at the transmission site, places that are similarly used by humans (see below). Iijima et al. (1971) necropsied 24 dogs in Khong Town

and found adult worms in 7. Many of the worms were in the mesenteric veins of the large intestine and in the portal vein ; smaller numbers were recovered from mesenteric veins of the small intestine. Sornmani et al. (1971) examined 46 dogs on Khong Island by taking fecal specimens directly from the rectum for direct smears and formalin-ether concentrations ; 5 of 46 (10.9%) were positive for *Schistosoma*.

The results of the exposure of two dogs to cercariae from experimentally infected *L. aperta* were reported by Sornmani et al. (1973) ; one dog exposed to 124 cercariae by loop application began to show eggs in the feces after 40 days ; a second dog receiving 214 cercariae was positive after 46 days.

Others : No other reservoir host of the Mekong *Schistosoma* has yet been identified. The most common domestic animal on Khong, after the dog, is the water buffalo, *Bubalus bubalis*. Since buffalo were often seen submerged in the shallow water of the transmission site at Ban Xieng Wang, they were well placed to pick up the infection if possible. On the basis of stool concentration and the hatching technique, Schneider et al. (1975) reported that 103 buffalo were parasitologically negative for eggs of the Mekong *Schistosoma* ; this represented virtually all buffalo in Khong Town and about one-tenth of the buffalo population of the entire island.

Cows were transients on Khong Island ; 43 were awaiting transport to the slaughterhouse in Paksé in 1973 and were examined parasitologically but no schistosome eggs were found (Kitikoon et al., 1975). Pigs on Khong, kept in pens, were only rarely seen loose in the yard ; none of 15 pigs in and near Khong Town were positive for eggs of *Schistosoma* (Kitikoon et al., 1975).

Wild rats proved to be relatively sparse in the vicinity of Khong Town during a field survey conducted in March, 1973. No schistosome infections were found upon perfusing 103 specimens, including 10 Lesser bandicoot rats (*Bandicota savilei*), 12 Polynesian rats or «house mice» (*Rattus exulans*) and 81 roof rats (*Rattus r. molliculus*).

Table 3 summarizes available data on natural infections in animals on Khong.

Discussion

It is seen that the pattern of transmission of Mekong schistosomiasis differs in many important details from that of the «classical» disease that occurs in other Asian regions. The amphibious *Oncomelania* snails are not involved in Southeast Asia and transmission therefore does not occur in their typical habitats, i.e., rice fields, drainage ditches, wet grass plots, or seepage areas. Rather, transmission is in the Mekong River and the transmitting snail, *Lithoglyphopsis aperta*, is totally aquatic.

Thus, the technology that has been worked out for the control of schistosomiasis in China, Japan, Philippines, and Indonesia, based on the bionomics of *Oncomelania*, cannot be applied in the lower Mekong basin.

Control, nevertheless, must be approached primarily through the snail. Although a beginning has been made, there are many gaps in our knowledge of the ecology of this snail and the epidemiology of the disease. Transmission is thought to be seasonal because the snails can be collected in abundance only during the dry season months extending from mid-March to early June; however, experimental evidence that the river may be safe during other months has not been

systematically sought. The fate of the snails during the period of high water remains mysterious since normal collecting methods are useless in the Mekong River during the rainy season. We do not know why they are able to appear in such large numbers so quickly in the dry season or what governs the variability in their numbers from one year to the next. Their taxonomy requires further study, as does that of the entire family hydrobiidae, and in *L. aperta* we have the apparent anomaly of sympatric races which can only be explained in terms of disjunct maturation. The difficulty of access to many areas of the lower Mekong river and to most of its tributaries leaves us with an incomplete and unsatisfactory view of geographic distribution. Since the snails cannot yet be cultivated in the laboratory in sufficient numbers to permit experimentation, certain types of work such as molluscicide testing must await the advent of the dry season when snails can be gathered in the wild.

In spite of these difficulties, a sufficient basis clearly exists for the beginning of efforts to control schistosomiasis on Khong Island. Recognizing this, the Mekong Committee has initiated a pilot program with the goal of achieving a measurable reduction in transmission in Khong Town within a 3-year period. The pilot project consists of 2 phases, including the following courses of action: i) training, and ii) implementation and evaluation.

i) *Training*. In Laos, there is a recognized lack of personnel trained in techniques of parasitological surveillance. However, technicians are needed well in advance of starting any control measures in order to obtain base-line data on the population at risk. They will also measure the results of control efforts. Under the

TABLE 3. Examination of domestic animals and wild rodents in the vicinity of Khong Town for infection with the Mekong *Schistosoma*.

Host	Species	Number examined	Positive		Method of examination *	References
			Number	%		
Dog	<i>Canis familiaris</i>	24	7	29	necropsy	Iijima <i>et al.</i> , 1971
Buffalo	<i>Bubalus bubalis</i>	46	5	11	DS & FEC	Sornmani <i>et al.</i> , 1971
		69	0	—	Watanabe conc.	Iijima & Garcia, 1967
Pig	<i>Sus scrofa</i>	103	0	—	MIFC & hatching	Schneider <i>et al.</i> , 1975
Cow	<i>Bos taurus</i>	15	0	—	MIFC & hatching	Kitikoon <i>et al.</i> , 1975
Polynesian rat (= "house mouse")	<i>Rattus exulans</i>	43	0	—	MIFC & hatching	Kitikoon <i>et al.</i> , 1975
		45	0	—	necropsy	Iijima & Garcia, 1967
Roof rat	<i>Rattus r. molliculus</i>	12	0	—	necropsy & perfusion	Kitikoon <i>et al.</i> , 1975
Lesser bandicoot rat	<i>Bandicota savilei</i>	8	0	—	necropsy	Sornmani <i>et al.</i> , 1971
		81	0	—	necropsy & perfusion	Kitikoon <i>et al.</i> , 1975
		10	0	—	necropsy & perfusion	Kitikoon <i>et al.</i> , 1975

* DS = direct smear
 FEC = formalin ether concentration
 MIFC = merthiolate iodine formalin concentration

auspices of the Mekong Committee it has been proposed that technician training be done at the Government Hospital Laboratory on Khong Island.

ii) *Implementation and Evaluation.*

The Mekong Committee has proposed to establish a pilot control program at Khong Island aimed at reducing transmission. Proposed control measures fall into two categories: those that might be implemented immediately and those that would require preliminary research.

Control measures to be applied initially comprise:

- a) environmental sanitation, including water supply and latrine construction;
- b) health education;
- c) snail control by engineering improvements at the shore of Khong Town. Additional control measures (which must, however, await the results of further research before they can be adopted) will include:
- d) snail control using molluscicides, and
- e) drug treatment trials in animals and man.

In addition to the above, there is a recognized need for certain basic research which may be applicable to control measures, particularly with regard to the aquatic ecology, geographic distribution and laboratory cultivation of the transmitting snail and its relatives. Such research is also being supported by the Mekong Committee in the context of the control project.

In connection with item *ii-c*, it has been proposed to alter the physical conditions at the transmission site which permit the juxtaposition of snails and people. While the final form of such im-

provements has yet to be decided, initial suggestions included the destruction of the peninsula and some of the small islands in the vicinity of the bathing area at Ban Xieng Wang and the construction of an embankment along the shore of Khong Town which would permit access to the river only at safe places. However, feasibility studies for these changes have not yet been carried out. Contracts for some phases of the work have been let between the Mekong Committee and the University of Lowell (Massachusetts), the Faculty of Tropical Medicine (Bangkok), and the Thomas A. Dooley Foundation, Inc. (Laos).

With the unsettled state of political affairs in Laos, it is now apparent that the original time-table for completion of these projects cannot be realized. Work dealing with molluscicide testing and basic studies on snail ecology have commenced and are being actively pursued at the Faculty of Tropical Medicine in Bangkok. However, it now appears unlikely that the training of technicians at the Government Hospital on Khong Island, the environmental sanitation, or the engineering improvements of the shoreline will be carried out through the contracts as originally envisioned. It would seem imperative to find other means, and perhaps new sources of funding, to complete these efforts which at this time are likely to answer most of the remaining questions concerning control of transmission of Mekong schistosomiasis.

Summary

Human schistosomiasis is transmitted in Southern Laos and Northern Cambodia in two known localities on the Mekong River; there may also be an extension of transmission to the Mun River in Northeast Thailand, near its confluence

with the Mekong. Cases reported from Southern (peninsular) Thailand appear on the basis of egg morphology to be related to the Mekong parasite but no transmitting snail is yet known and the relationship is obscure. The meaning of isolated apparently autochthonous cases from West Malaysia and Northern Thailand cannot be stated. Schistosomiasis in Sulawesi (Celebes), Indonesia, is probably unrelated to the Mekong *Schistosoma*.

Prevalence figures for Laos are based on three clinical studies, two of which were undertaken by WHO (1966-67; 1968-69) and one by the Faculty of Tropical Medicine in Bangkok (1969). On the basis of parasitological results, prevalence in Khong Town averaged 27.8% and on Khong Island and nearby areas 13.9% in all age groups. Prevalence in primary and secondary school children was higher, 30 to 40% in Khong Town. No egg-passing cases were detected in Vientiane, although skin-test positives were found. In Pakse no «home-grown» cases are known; investigators found 3 egg-positive students who had come from Khong Island.

Transmission on Khong Island occurs in the Mekong River adjacent to the Ban Xieng Wang section of Khong Town, in a popular bathing area and next to a defecation site.

The transmitting snail is *Lithoglyphopsis aperta* (Hydrobiidae: Triculinae) which, in April, 1972, was dominant in

the river near Khong Town. Three races of the species are known: alpha, beta and gamma. The gamma race is the «tiger-striped» snail first identified as a transmitter.

Dogs are the only known natural reservoir hosts of the Mekong *Schistosoma*. Natural infections were sought but not found in buffalo, cows, pigs, and wild rats on Khong island.

A pilot control program, under the guidance of the Mekong Committee, is comprised of: i) technician training and ii) implementation measures: the latter include initial control measures (installation of piped water and latrines; health education; engineering improvements at Khong Town shoreline) and additional control measures to be based on results of research on molluscicides and drug trials, as well as continuing research on the aquatic ecology of the snails. The aim of the pilot program is a measurable reduction in transmission of schistosomiasis in Khong Town.

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CONDITIONS NATURELLES DE LA TRANSMISSION DE *SCHISTOSOMA MANSONI* EN GUADELOUPE (ANTILLES FRANÇAISES)

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L'étude des conditions naturelles de la transmission de la bilharziose en Guadeloupe a montré que les eaux continentales présentaient, à ce point de vue, une valeur très inégale. Les canaux creusés autrefois pour l'alimentation en eau des moulins, et maintenant surtout utilisés pour l'irrigation, se sont avérés particulièrement dangereux. Situés exclusivement dans la partie montagneuse de l'île, ils constituent une source permanente d'infestation pour la population qui les utilise pour les cultures et les besoins domestiques. L'étude présentée ici se limite à ce type de biotope, même si d'autres milieux sont capables, en Guadeloupe, d'assurer la transmission de la maladie.

Les Canaux

Leur utilisation originelle nécessitait un courant et un débit assez forts pour entraîner un moulin. Quelques-uns sont encore exploités pour broyer la canne, décortiquer le café ou faire de la glace. Bien entretenus, ils sont impropres à l'établissement de colonies de *Biomphalaria glabrata* dans leur cours principal, mais le deviennent parfois dans les fuites et dérivations, en particulier dans la partie du cours située en aval du moulin, si le canal ne retourne pas rapidement à la rivière et a le temps de s'assagir.

Malheureusement, lors de la ruine ou de la modernisation des exploitations qu'ils desservaient, beaucoup de canaux ont été déviés de leur utilisation initiale.

L'irrigation des cultures ou l'utilisation domestique ont justifié un entretien partiel, suffisant à leur persistance, mais diminuant beaucoup leur débit. C'est dans ces conditions que ces canaux sont devenus des biotopes particulièrement favorables à *B. glabrata*. Leur régime régulier tout au long de l'année, leur contact étroit avec la population, leurs paramètres écologiques en font actuellement une source de contamination particulièrement dangereuse.

Parfois longs de plus de dix kilomètres, ces canaux trouvent toujours leur origine dans une «prise d'eau», simple mur de pierre dérivant une partie du courant de la rivière qui les alimente.

La première partie de leur cours est rapide, le débit est assez fort. On y trouve la faune normale de la rivière, mais aucun Planorbe. Des subdivisions successives, des dérivations, volontaires ou non, font que le canal devient de plus en plus faible, son courant de plus en plus lent. La faune des rivières disparaît et des Mollusques apparaissent (Physes, Ampullaires). Un peu plus bas on trouve les premiers Planorbes.

Les canaux se terminent de diverses manières. Certains aboutissent à la mer. D'autres sont entièrement absorbés par l'irrigation. Beaucoup enfin retournent à la rivière, après un trajet de longueur variable.

L'étude de toutes les branches de ces canaux, sur toute leur longueur, permet

généralement de trouver l'emplacement des colonies de *B. glabrata*. L'altitude de la station dépend de caractéristiques propres au canal, essentiellement débit et courant. Il arrive que le canal se termine avant d'avoir réuni les conditions favorables aux Planorbes. C'est le cas en particulier de certains canaux encore exploités pour leur énergie hydraulique. Il arrive aussi que le canal se termine, en pleine zone de pullulation des Planorbes, en se jetant dans une rivière. Dans ce cas, les Mollusques, emportés dans la rivière meurent très rapidement et on trouve leurs coquilles vides à proximité de l'aboutissement du canal, dans le lit de la rivière. Cependant, si les Planorbes sont infestés, les cercaires seront également emportées dans l'eau de la rivière, qu'elles contamineront.

Beaucoup de ces canaux, dans la partie inférieure de leur cours, traversent une agglomération à laquelle ils apportent une eau limpide et fraîche. Celle-ci n'incite pas à la méfiance et ces eaux sont très exploitées pour les jeux des enfants, le lavage du linge ou de la vaisselle. La nuit, clandestinement, on y rejette les eaux usées et les excréments car, trop souvent, le canal constitue le seul égoût disponible. Généralement, les niveaux de densité maximale de Mollusques et de concentration humaine maximale coïncident, si bien que le cycle de *Schistosoma mansoni* se déroule dans les conditions les meilleures.

Testés en laboratoire, les Mollusques de ces canaux se sont montrés souvent lourdement infestés par le parasite. C'est pour tenter d'approcher la valeur épidémiologique de cette infestation qu'a été entreprise l'étude des cercaires dans ce biotope particulier.

Matériel et Méthodes

Deux techniques ont été utilisées simultanément : l'une de filtration directe

des eaux, permettant d'opérer des comptages de cercaires, l'autre de bain de souris, permettant de contrôler l'appartenance des cercaires décomptées à l'espèce *S. mansoni*.

1. Filtration directe des eaux

Cette technique est une transposition de celle qui a été utilisée à Ste Lucie par Sandt, 1973. Un groupe électrogène fournit l'énergie nécessaire au fonctionnement d'une pompe à vide. Ainsi est assurée l'aspiration dans un bidon plastique de 30 litres gradué, surmonté d'un entonnoir type Buchner, qui reçoit des filtres en fibres de verre (Fig. 1). L'eau à filtrer est directement versée sur le filtre. La faible turbidité des eaux étudiées permet de faire passer environ 10 litres par filtre, ce qui est suffisant pour obtenir des chiffres valables. Le volume exact est donné, à chaque opération, par la graduation du bidon. Les filtres sont colorés et fixés par du Lugol puis rapportés au laboratoire pour étude à la loupe binoculaire.

2. Bain de souris

Afin de contrôler l'appartenance des cercaires décomptées par la technique précédente, et aussi de se rapprocher le plus possible des conditions de l'infestation humaine, des souris ont été systématiquement baignées en même temps que l'on réalisait des filtrations.

Le bain, d'une durée standardisée d'une heure, est réalisé grâce à l'emploi de très petites cages munies de flotteurs (Fig. 2). Dans ces cages, l'animal conserve une certaine mobilité. Les flotteurs sont réglés de telle sorte que le niveau de l'eau soit aux environs du milieu de la cage, si bien que la souris respire à l'air libre, mais ne peut éviter qu'une partie importante de son corps baigne dans l'eau. Généralement, trois souris sont baignées simultanément, en trois emplacements

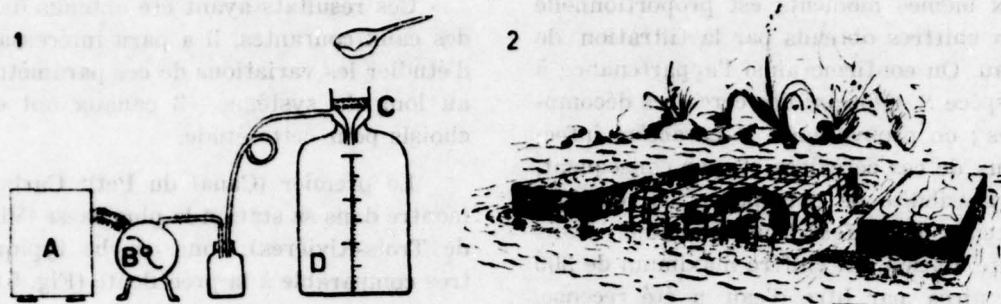


Fig. 1. Schéma du dispositif de filtration. A, groupe électrogène; B, pompe à vide; C, Entonnoir avec filtre en fibres de verre; D, bidon gradué.

Fig. 2. Cages munies de flotteurs pour bain de souris.

assez proches du point de prélèvement de l'eau destinée à la filtration directe.

Après 5 semaines, les animaux sont sacrifiés et le système porte perfusé. Les schistosomes, encore immatures, sont comptés, et la moyenne établie entre les animaux baignés au même endroit et à la même heure. Un délai plus long permet l'apparition des œufs, mais les adultes deviennent plus rares et le nombre des vers retrouvés cesse d'être proportionnel aux décomptes de cercaires dans l'eau.

3. Utilisation des techniques

Une première série de prospection a été conduite en 1974. Chaque biotope était étudié pendant une heure, par deux filtrations et le bain d'un lot de souris, réalisés à un moment variable de la journée. Les résultats ont été très décevants ne permettant d'obtenir que de faibles concentrations de cercaires, même en des points grouillant de Planorbes infestés. Par ailleurs, la température de l'eau mesurée systématiquement pendant l'opération, variait considérablement d'une station à l'autre, et semblait n'avoir aucun rapport avec la densité en cercaires.

Aussi, une seconde série de prospections a-t-elle été entreprise, étudiant une seule station tout au long de la journée.

Tandis qu'un thermographe enregistrerait la température de l'eau, les souris étaient remplacées toutes les heures aux mêmes endroits et l'eau filtrée toutes les demi-heures.

Résultats

Dès le premier échantillonnage continu (Fig. 3), la densité des cercaires dans l'eau se révéla sujette à de grandes variations dans la journée. Faible ou nulle le matin de bonne heure, elle croît en même temps que la température pour atteindre un maximum et retomber, tandis que la température reste haute. Ainsi est réalisé un pic de densité dont le démarrage correspond au franchissement par la courbe de température d'un niveau critique, situé aux alentours de 26°5 C.

Cette température ne doit pas être considérée comme un seuil car des émissions de cercaires existent pour des températures plus basses. Cependant dans toutes les stations étudiées, quel que soit le niveau auquel parvient le maximum de la courbe, c'est toujours à partir du moment où l'eau atteint 26°5 que les cercaires deviennent abondantes, pour se raréfier ensuite.

La courbe de la figure 4 montre en outre que l'infestation des souris baignées

aux mêmes moments est proportionnelle aux chiffres obtenus par la filtration de l'eau. On confirme ainsi l'appartenance à l'espèce *S. mansoni* des cercaires décomptées ; on prouve enfin le caractère infectieux de ces cercaires et, par conséquent, la possibilité de transposer les résultats obtenus à l'infestation humaine. Dans cette station, un chiffre maximum de 300 cercaires par litre d'eau a été recensé, tandis que chez les souris baignées à la même heure, 600 schistosomes étaient décomptés.

Ces résultats ayant été obtenus dans des eaux courantes, il a paru intéressant d'étudier les variations de ces paramètres au long du système. 3 canaux ont été choisis pour cette étude.

Le premier (Canal du Petit Carbet) montre dans sa station la plus basse (Ville de Trois-Rivières), une courbe typique, très comparable à la précédente (Fig. 5).

L'étude de la partie sus-jacente du canal est synthétisée par la figure 6. A la prise d'eau, la température est remarqua-

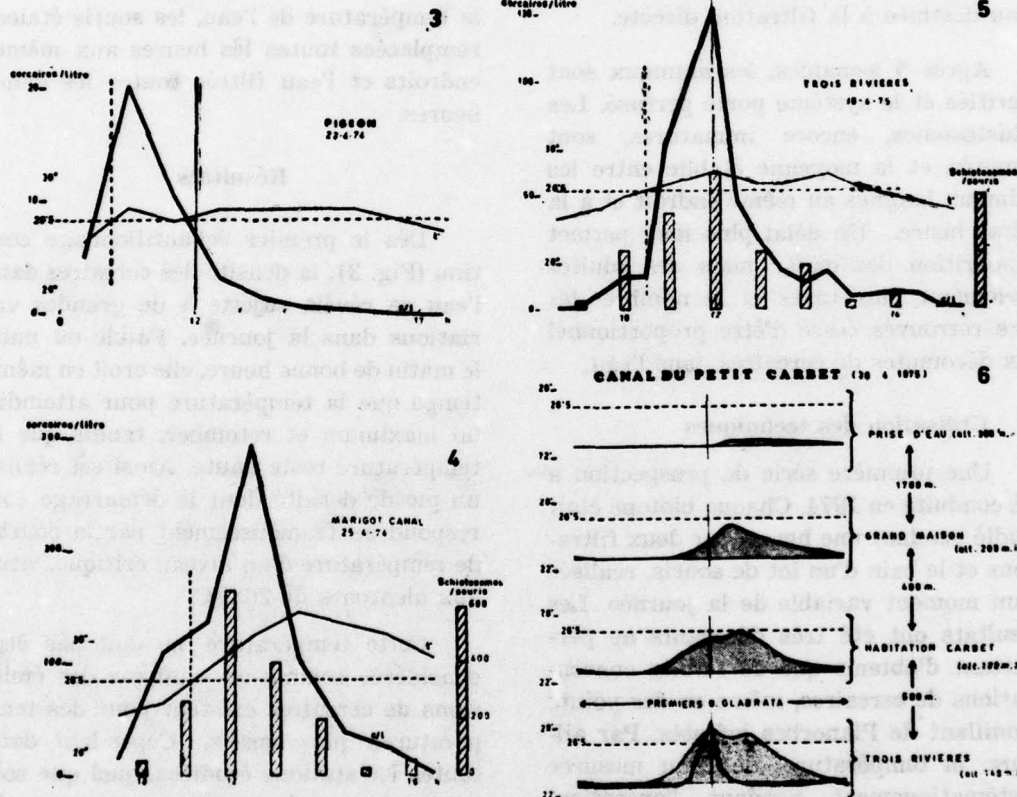


Fig. 3. Cercaires par litre d'eau filtrée: variation en fonction de la température.

Fig. 4. Station très infestée: 300 cercaires par litre d'eau à 12 h 30. Les souris baignées de 12 à 13 h sont massivement infestées.

Fig. 5. Station typique sur le canal du petit Carbet.

Fig. 6. Diagrammes de quatre stations du Canal du petit Carbet. La température ne dépasse 26°5 que dans la station la plus basse. C'est la seule qui soit infestée (pic de cercaires à midi).

blement constante : 23° la nuit, 23°5 aux heures les plus chaudes de la journée. A l'habitation Grand Maison, l'augmentation de la température diurne est déjà importante, le maximum atteignant 26° vers 14 h. Pourtant 1700 m seulement séparent ces deux points ; et la dénivellation de 160 m (10% environ) indique un courant rapide. A l'habitation Carbet, la température atteint 26°5, mais il n'y a pas encore de *Biomphalaria*, et aucune cercaire n'est retrouvée. Juste au-dessous de cette station apparaissent les premiers Mollusques. La dernière courbe est celle de Trois-Rivières, qui est, comme nous l'avons vu, typique.

Deux hypothèses peuvent se dégager de ces résultats :

- 1) *B. glabrata* n'apparaît que lorsque la température atteint 26°5. Cette hypothèse est fautive, car l'espèce a été trouvée dans des biotopes d'altitude, où l'eau est beaucoup plus froide. Il s'agit donc ici d'une coïncidence.
- 2) *B. glabrata* étant présent, les cercaires ne sont émises en abondance suffisante pour avoir une valeur épidémiologique que si la température atteint 26°5. Ceci recoupe les données de la courbe quotidienne dans les stations où la température croise et dépasse cette limite. Cette hypothèse paraît vraisemblable, mais ne pourra être confirmée que par l'étude de plusieurs stations présentant une température maximale < 26°5 et offrant par ailleurs toutes les conditions nécessaires au cycle (*B. glabrata* abondants, souillure de l'eau par des déjections humaines infestées). Quoi qu'il en soit, confiante en cette hypothèse, l'équipe entière s'est baignée

plusieurs fois, à des heures différentes, dans la prise d'eau, sans qu'aucune bilharziose ait été contractée !

Le second canal étudié est schématisé par la figure 7. Dès la prise d'eau (altitude 55 m seulement), la température dépasse largement 26°5 pendant plusieurs heures dans la journée. On note également que les minima nocturnes sont beaucoup plus élevés. Les premiers mollusques n'apparaissent cependant que beaucoup plus loin, après la distillerie, démontrant ainsi à nouveau que le facteur limitant l'extension de *B. glabrata* n'est pas la température.

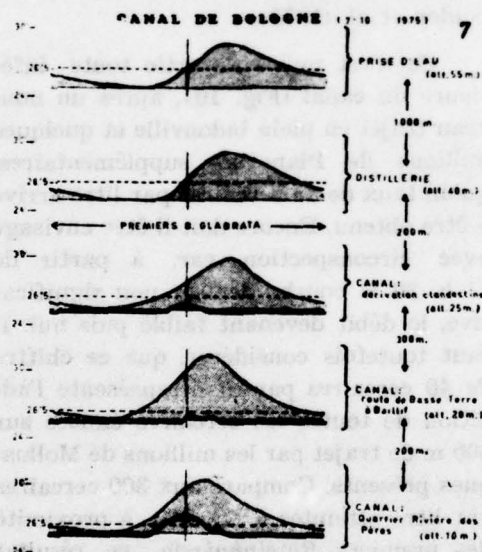


Fig. 7. Diagrammes de cinq stations du canal de Bologne. Dès la prise d'eau, la température dépasse 26°5 plusieurs heures par jour. Dans la zone hébergeant les mollusques, la température de l'eau descend peu au-dessous de 26°5, et pendant quelques heures seulement. Le pic de cercaires est faible.

200 m après la distillerie, alors que l'eau du canal est passée sur des milliers de *Biomphalaria glabrata*, en bordure d'habitations, la présence des cercaires

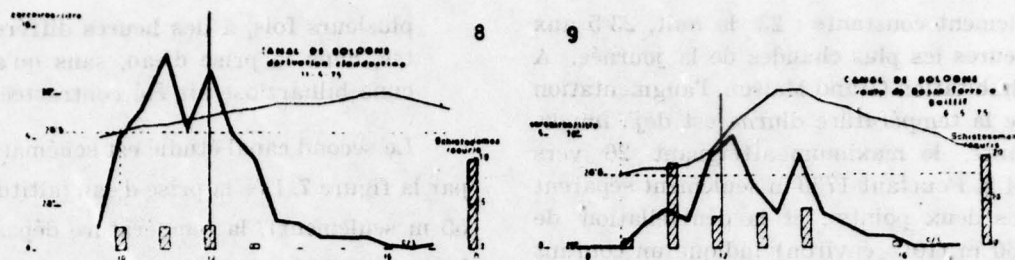


Fig. 8. Station du Canal de Bologne: température élevée, infestation faible.

Fig. 9. Station du Canal de Bologne.

est très faible (Fig. 8). Il en va de même à l'endroit où le canal coupe la route de Basse-Terre à Baillif (Fig. 9) après 300 m de parcours pullulant de Planorbes et au milieu des cases de l'une des populations les plus misérables de l'île et les plus infestées de bilharziose (80% d'après Tribouley et al. (1975)).

Ce n'est qu'à la partie toute inférieure du canal (Fig. 10), après un nouveau trajet en plein bidonville et quelques millions de Planorbes supplémentaires, qu'un taux de 40 cercaires par litre arrive à être obtenu. Encore doit-il être envisagé avec circonspection car, à partir de 11 h. 30 la courbe devient non significative, le débit devenant faible puis nul. Il faut toutefois considérer, que ce chiffre de 40 cercaires par litre représente l'addition de toutes les cercaires émises sur 600 m de trajet par les millions de Mollusques présents. Comparé aux 300 cercaires par litre atteintes à Marigot, à proximité des premiers *Biomphalaria*, ce résultat apparaît comme extrêmement faible (encore qu'il présente, comme le montre l'infestation des souris, une indiscutable valeur épidémiologique).

Nous ne pouvons, sur ces résultats, fournir une explication certaine à cette constatation. Toutefois, une hypothèse très intéressante ressort de la comparaison des diagrammes. Dans le canal de Bologne, les températures minimales sont

proches de 26°5 et le temps pendant lequel la courbe reste au-dessous de cette valeur est court (4 à 5 heures). Au contraire, dans le canal du Petit Carbet, les minima sont très au-dessous de 26°5 et le temps pendant lequel la courbe reste au-dessous de cette valeur est long. Cette phase froide du cycle nycthémeral est peut-être indispensable au succès de l'infestation du Mollusque. D'ailleurs lorsqu'on réalise au laboratoire le cycle expérimental de *Schistosoma mansoni*, on sait qu'il ne faut exposer les Mollusques infestés ni trop longtemps ni trop souvent aux températures qui permettent l'éclosion des cercaires, sous peine d'avoir une forte mortalité.

Cette hypothèse aurait en outre l'avantage d'expliquer la négativité maintes fois constatée de toute une série de biotopes guadeloupéens, fourmillant de *B. glabrata*, mais stagnants, et par suite non-soumis aux variations nycthémerales que connaissent les canaux.

Le troisième canal étudié comporte, 250 m après la prise d'eau, une station typique, encore que le taux maximum obtenu ne soit pas très élevé. Dans ce canal, on a essayé de suivre la destinée des cercaires au-dessous de la station typique (Fig. 11), et alors que, sur 500 m, les Mollusques étaient extrêmement nombreux. Grande a été la surprise de constater, dans la station inférieure, une den-

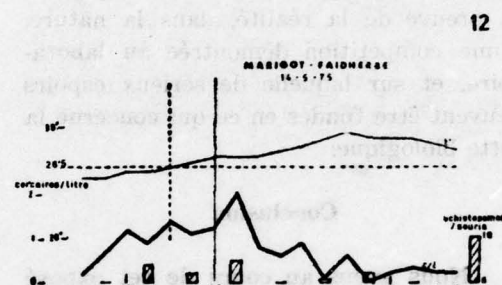
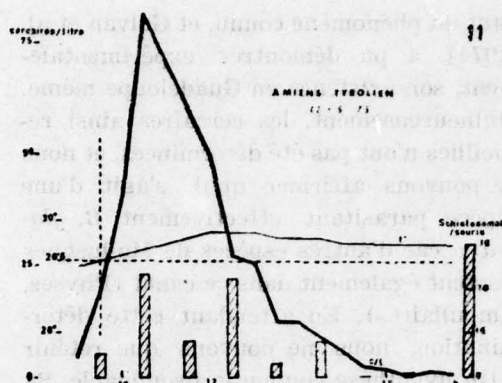
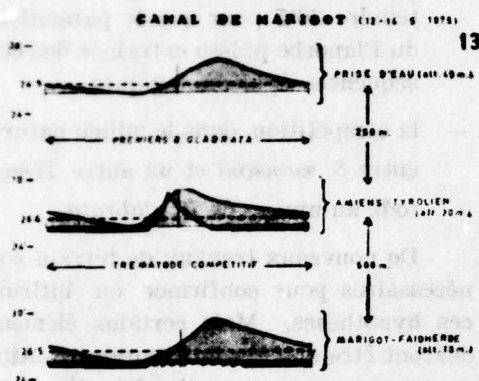
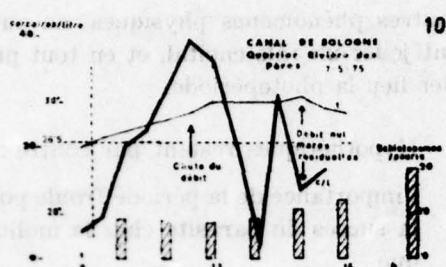


Fig. 10. Station la plus basse du Canal de Bologne: malgré l'accumulation des cercaires provenant d'amont, la quantité de cercaires obtenue reste faible à la filtration. Il y a également des concentrations dans la journée (surtout net sur les infestations de souris).

Fig. 11. Station typique sur le canal de Marigot.

Fig. 12. Station atypique, [sans pic de concentration de cercaires, dans la partie basse du canal de Marigot.

Fig. 13. Diagramme comparatif des trois stations du canal de Marigot.

sité de cercaires très faible et très étalées dans la journée (Fig. 12). Malgré la présence de très nombreux *B. glabrata* au point étudié, il n'y a pas de pic d'émission, ce qui démontre l'incapacité dans laquelle se trouvent les Mollusques, en ce point, d'assurer significativement la maturation du parasite. Les cercaires constatées sont certainement celles qui proviennent de la station sus-jacente, emportées avec le «drift». L'étalement au cours de la journée doit être mis sur le compte de l'inégale rapidité du courant au centre et sur les bords du canal, entraînant le ralentissement de la dérive de certaines cercaires.

Il est d'ailleurs possible, le décompte ayant cessé à la tombée de la nuit, qu'ait été manqué le passage des eaux véhiculant le maximum de parasites.

Quoi qu'il en soit, 500 m au-dessous d'une station active, les Mollusques toujours présents, n'émettent plus de cercaires (Fig. 13). Une hypothèse explicative découle de la constatation, sur les filtres, de la présence d'innombrables cercaires à queue non-bifide, qui remplacent en quelque sorte les cercaires de *S. mansoni*. La compétition entre Trématodes à l'intérieur du Mollusque-hôte est mainte-

nant un phénomène connu, et Golvan et al. (1974) a pu démontrer expérimentalement, son existence en Guadeloupe même. Malheureusement, les cercaires ainsi recueillies n'ont pas été déterminées, et nous ne pouvons affirmer qu'il s'agit d'une espèce parasitant effectivement *B. glabrata*, car d'autres espèces de Mollusques existent également dans ce canal (Physes, Ampullaires). En attendant cette détermination, nous ne pouvons que retenir cette hypothèse comme vraisemblable. Sa confirmation apportera, nous l'espérons, la preuve de la réalité, dans la nature, d'une compétition démontrée au laboratoire, et sur laquelle de sérieux espoirs peuvent être fondés en ce qui concerne la lutte biologique.

Conclusion

Nous avons au cours de cet exposé mêlé ce qui était résultats des observations de terrain et hypothèses induites. Il était en effet nécessaire de rapprocher les uns et les autres, les premiers justifiant les secondes. Il serait très dangereux d'assimiler ce qui reste hypothétique et ce qui est le résultat de mesures matérialisées par les courbes.

Indiscutables sont la chronologie de la courbe de densité des cercaires et les rapports de celle-ci avec la température, dans les biotopes étudiés. Rien ne prouve par contre que dans l'autres biotopes, et en particulier dans les eaux stagnantes,

d'autres phénomènes physiques ne puissent jouer un rôle capital, et en tout premier lieu la photopériode.

Hypothétiques restent par contre :

- l'importance de la période froide pour la succès du parasite chez la mollusque
- la nécessité pour la température d'atteindre 26°5 pour que le parasitisme du Planorbe puisse entraîner des conséquences épidémiologiques
- la compétition, dans le milieu naturel, entre *S. mansoni* et un autre Trématode au niveau de *B. glabrata*.

De nouveaux travaux de terrain sont nécessaires pour confirmer ou infirmer ces hypothèses. Mais certains éléments devront être obtenus au laboratoire. Ainsi se trouve une nouvelle fois illustrées l'étroite collaboration indispensable entre le travail sur le terrain, mené d'une manière aussi rigoureuse et quantitative que possible, et l'expérimentation au laboratoire. La confrontation des résultats des deux approches, sans complaisance ni indulgence, décèle au mieux les faibles des raisonnements et les lacunes des bases expérimentales. A ce prix pourraient être progressivement élucidés des mécanismes aussi complexes que ceux qui assurent la transmission, dans les conditions naturelles, de la bilharziose à *Schistosoma mansoni*.

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ABSTRACT**FIELD CONDITIONS OF THE TRANSMISSION OF
SCHISTOSOMA MANSONI IN GUADELOUPE
(FRENCH WEST INDIES)**

S. mansoni cercariae were studied in natural waters by mouse immersion and a technique of direct filtration. Very high densities were obtained in some cases (maximum 300 per litre). In the island of Guadeloupe, the infecting areas are mainly small canals where the current is not strong. The water, which comes from the mountains, is relatively cold at night and gets hot by day. Under these conditions, the cercarial output occurs when the water temperature reaches 27°C. After reaching a maximum, the cercarial den-

sity decreases very quickly, even if the temperature remains high. If the water temperature does not reach 27°C, there is no cercarial output, or one so low that it has no epidemiological significance. If the water temperature is always high, as in the case of ponds, for example, natural transmission does not occur. In the biotope studied, it appears that the alternance of a low night temperature (< 27°C) and a high day temperature (> 27°C) in natural waters is necessary for the transmission of the parasite.

**SCHISTOSOMIASIS IN THE SUDAN :
HISTORICAL BACKGROUND AND THE PRESENT MAGNITUDE
OF THE PROBLEM**

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Schistosomiasis is an ancient disease in the Sudan and is thought to have started in the country centuries before the Christian era and to have been introduced by ancient Egyptian traders (Archibald, 1933). Historical links existed between the northern part of the Sudan and the southern regions of Egypt, an empire compassing the two areas as far back as the 7th and 8th centuries B.C. These connections probably resulted in free movement and common agricultural practices which may have spread the disease to the Sudan. But, unfortunately, reliable reports about the incidence of the disease in the various regions of the country are relatively recent. Christopherson (1918) thought that schistosomiasis was endemic in all provinces of the country except the Red Sea area. He received patients in Khartoum hospital and first used tartar emetic in the treatment of schistosomiasis in Sudan (Christopherson, 1918).

The first attempt to define the endemic areas of the country was made in the 1927 annual medical report. These areas were identified as Wadi Halfa and parts of the northern province, the White Nile and parts of the Blue Nile province, the Nuba mountains and parts of Kordofan and Darfur provinces. Humphreys (1932), reviewing schistosomiasis in the Gezira area, mentioned that before the Sennar Dam was built in 1924 a focus of

Schistosoma haematobium was found in a small region on the Blue Nile province. This record was the only evidence of infection. Later Archibald (1933) reported that the disease was present in 12 out of 15 provinces, *S. haematobium* being present in 10 and *S. mansoni* in 6 provinces. He also reported finding various species of «Planorbis» in the Blue and White Nile provinces. *Bulinus* species were reported to be present in the Blue Nile province, and in the Nuba mountains in rain water collections. Later, with extension of agriculture, the institution of perennial irrigation by pump schemes and especially by the building of the Sennar Dam, together with the creation of a large network of irrigation canals, the prevalence of the disease increased steadily. The expansion of agriculture, its type and the problems posed vary in the different parts of this large country, and it is intended in this paper to discuss the various regions separately.

Central Sudan

**A. The Gezira Irrigated Area
South of Khartoum**

1. Description

This is the area where the greatest expansion in irrigation occurred in the Sudan. It is the largest cotton irrigation project in the world and produces the Sudan's most important cash crop. It

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covers over five million acres, with more than three million acres suitable for cultivation. There are about 200 villages in the area and a few towns, mainly along the Blue Nile River. Formerly the area was a plain with a scanty seasonal rainfall occurring mainly in the period July to September. Water was drawn from wells, except in the villages lying along the river. The environment completely changed in this area when the artificial canal irrigation scheme started in 1934 following the building of the Sennar Dam. A large network of canals was constructed throughout the agricultural scheme.

At the present time a chlorinated water supply tank is installed in most villages, but occasionally it is not functioning. Most of the time the people used the nearby irrigation canals for their drinking water and for washing. The children are usually attracted to the canals for swimming and sometimes forced to these sites by the hot weather. The canals are heavily infected with *Biomphalaria* and *Bulinus* snails.

Sanitation in most of the villages is poor, only a few shallow pit latrines exist and many people urinate and defaecate outside the houses or on the edges of the canals.

2. *The changing pattern of the prevalence of schistosomiasis in the Gezira*

In this region, Greany (1952a,b) carried out a systematic survey in 1948-49. He examined over 80,000 individual urine and stool samples from the population using, for the former, centrifugation and, for the latter, a direct smear which if negative was followed by a simple sedimentation technique.

Greany showed that the prevalence of both infections in both sexes was highest in children of the 5-10 year and 10-15 year age groups and in young adults from 15-20 years old, and then fell gradually.

Greany's work also showed that nearly 9% of the total population examined was infected and that the proportion of those infected with *S. haematobium* and *S. mansoni* was similar. The highest percentage of infection with any species in any age group was under 15% and in those over 65 years it was only 1.7% in males and 0.7% in females. Following Greany's work there was a long gap in reported prevalence data and no systematic surveys were carried out till the present London-Khartoum Bilharzial Project. The findings reported here are based on my personal experience in the project. This study was carried out during the past three years in the northern part of the Gezira. It covered various villages, where a detailed census of the population was first carried out. This was followed by visiting the village and inviting all the people to attend for examination. Each subject was given a serial number, was asked standard questions and was then examined. Various investigations were carried out. I shall here mention some results concerning the prevalence of the disease. Stools were examined by the NaOH digestion technique and urines by the centrifugation method.

a) *Present prevalence of schistosomiasis in a village in the northern Gezira*

i. *Stool examination for S. mansoni.*

The data are derived from a survey of a village with a population of 2307, of whom 1747 attended, i.e., with an overall response rate of 75.7%. Fig. 1 shows that the prevalence rate rises steeply in both sexes to a peak of about 80% by the age of 20 and then falls gradually in both sexes, falling faster in females than males. The same pattern is reflected in the mean counts of eggs per g of faeces, Fig. 2 (Omer, 1975).

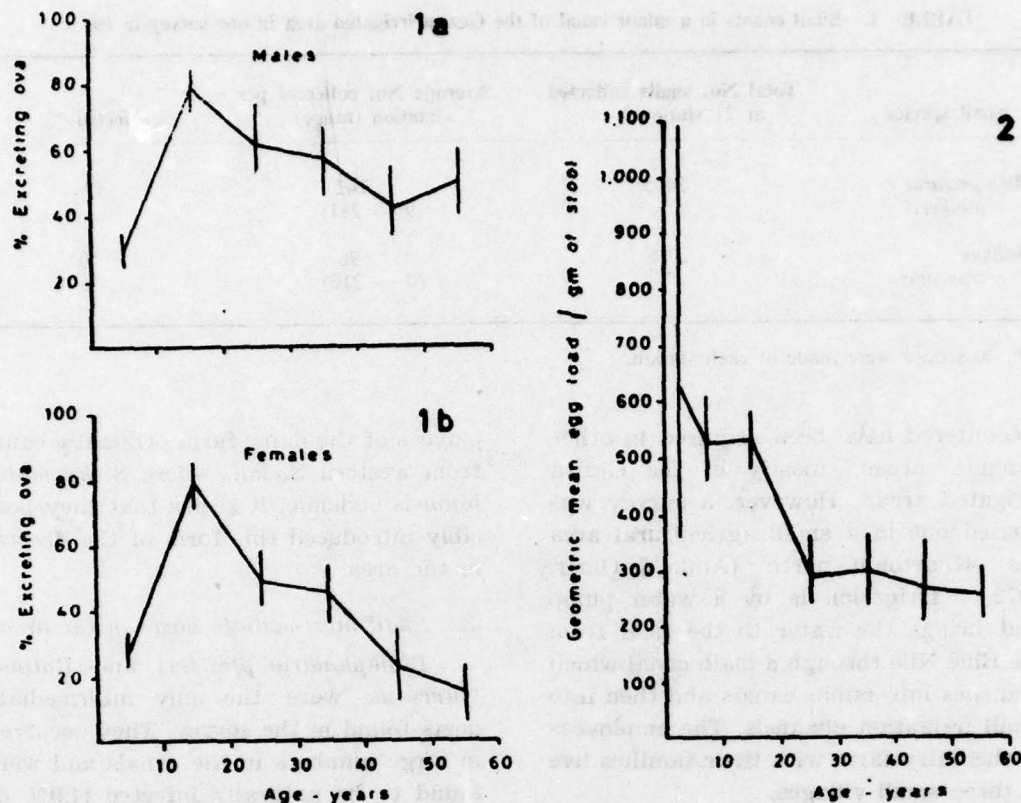


Fig. 1. Prevalence of *Schistosoma mansoni* infection in males and females by 10-year age groups in a Gezira village, Sudan (Vertical bars indicate 95% confidence limits).

Fig. 2. Geometric means of *Schistosoma mansoni* egg counts in stools of infected persons only, by 10-year age groups, in a Gezira village, Sudan (Vertical bars indicate 95% confidence limits).

ii. Urine examinations

Only four urine samples were found to contain ova of *S. haematobium*. No *S. mansoni* ova were found in the urine.

These findings show that in the last 25 years there has been a great increase in the incidence of *S. mansoni* infection in the Gezira irrigated area of the Sudan. This increase was linked to the great expansion in agriculture and the use of artificial canal irrigation. However, on the other hand, there is a definite drop in the incidence of *S. haematobium* infection in the same area. This is an interesting phenomenon which will be discussed later in relation to the survey in the Eastern Sudan.

b) Ecological studies on the snails transmitting schistosomiasis in the Gezira

Greany (1952a) reported on the types of snails encountered in the Gezira, mentioning various species of *Bulinus* and also «*Planorbis boissyi*». He listed other types of snails encountered.

Table 1 summarises snail counts in a minor canal of the Gezira during one survey in 1973.

B. Irrigated Area in Khartoum Province

1. Description

Many medical and public health authorities in the Sudan believe that schistosomiasis in Khartoum province is negligible and that most of the cases

TABLE 1. Snail counts in a minor canal of the Gezira irrigated area in one survey in 1973.

Snail species	Total No. snails collected at 21 stations*	Average No. collected per station (range)	Infected %
<i>Biomphalaria pfeifferi</i>	3405	162 (9 — 281)	12
<i>Bulinus truncatus</i>	2016	96 (0 — 210)	0

* 20 scoops were made at each station.

encountered have been acquired in other endemic areas, mostly in the Gezira irrigated area. However, a survey was carried out in a small agricultural area near Khartoum north (Amin & Omer, 1972). Irrigation is by a water pump that brings the water to the field from the Blue Nile through a main canal which branches into minor canals and then into small irrigation channels. The employees of the dairy farm with their families live in three small villages.

2. Prevalence of schistosomiasis

The survey showed that the prevalence of *S. haematobium* among the field workers in this area was 65% and that it was 44.1% among the school children aged 7-15 years. Non-field workers showed an infection rate of 36.9% while housewives showed an infection rate of only 2%. Children aged 2-6 years showed a prevalence rate of 3.4%. The examination of the children of a nearby school showed that of the 330 boys examined, 100 (30.2%) were infected with *S. haematobium* and 34 (10.3%) with *S. mansoni*.

This survey thus reveals that *S. haematobium* and *S. mansoni* are endemic in at least one focus in Khartoum province, since about 40% of the infected people had never left the area while the majority were born there. This agrees with the findings of Malek (1962). As the em-

ployees of the dairy farm originally came from western Sudan, where *S. haematobium* is endemic, it seems that they possibly introduced this form of the disease in the area.

3. Snail intermediate hosts in the area

Biomphalaria pfeifferi and *Bulinus truncatus* were the only intermediate hosts found in the survey. They occurred in large numbers in the canals and were found to be naturally infected (4.9% of 310 *Bulinus* snails but only 3 *Biomphalaria* out of 750 examined).

However, striking differences were noted as regards the infection rates in the three villages examined and the farm. Higher infection rates were found in the two villages with poor sanitation, which were close to the water courses, as compared to the 3rd village and to the children of Kober village which has a piped clean water supply and good sewage disposal. This shows that schemes irrigated by water pumps are important in the transmission of schistosomiasis in the Sudan.

C. Northern and Eastern Sudan

1. Description

The construction of the Aswan High Dam in Egypt resulted in flooding and submerging the land behind it. By 1964, a large and deep lake had formed of which

about 150 km were within the northern borders of the Sudan. As a result, over 50,000 Nubians living in the Wadi Halfa district of Northern Sudan were transferred and resettled in Khashm El Girba area, 600 miles away in Eastern Sudan (New Halfa). The magnitude of the problem surpassed any past experience of the kind in the Sudan, and was perhaps unique in the world. The Nubians in the new area faced social, ecological and environmental conditions completely different from what they had known. This, it was thought, would expose them to new diseases, an idea which stimulated me to the present study (Omer, 1973). The two regions are shortly compared in the following.

a) *The former home of the Nubians in the northern Nile Valley at Wadi Halfa*

This area comprizes the site of «Old Halfa», once the northernmost town in the Sudan, and 14 groups of villages. It is a narrow strip of cultivation along the Nile bordered by the desert. The most modern type of irrigation there was by a pump scheme but water was and is commonly lifted by «Sagia» or water wheels (i.e., a primitive way of irrigation). The climate is of desert type, hot in summer and cold in winter, with occasional showers in winter.

b) *The resettlement area (New Halfa) at Khashm El Girba, Eastern Sudan*

This area is a large plain (the Butana plain) on the west side of the River Atbara, about 400 km east of Khartoum. It has very good, fertile soil. The area is semi-arid, with an annual rainfall of 300-500 mm, which, however, varies considerably from year to year. The temperature varies from 41°C in May to 15°C in January with an average of 29°C. Before the resettlement scheme, it was sparsely populated by nomadic and semi-nomadic tribes. The Nubians are now resettled in about 30 villages and a town (New Halfa).

The irrigation system. From the reservoir of Khashm El Girba there arises a main canal which branches into major and minor canals; but unlike the Gezira area, where the entire system is based on gravity irrigation, pumps are brought into action to maintain the supply when the reservoir level falls below canal level.

2. *Results of the schistosomiasis survey in the two areas*

a) *Old Halfa district, Northern Province*

(i) *Urine examination*: Table 2 shows the infection of *S. haematobium* among

TABLE 2. Prevalence of *Schistosoma haematobium* infection among the Nubians in Old Halfa district, 1970.

Age group in years	Males			Females		
	No. examined	Infected		No. examined	Infected	
		No.	%		No.	%
0 — 5	99	—	—	82	—	—
6 — 10	134	3	2.2	84	2	2.3
11 — 15	150	17	11.3	123	12	9.7
16 and above	184	23	12.4	160	17	10.6
Total	567	43	7.5	449	31	6.8

the various age groups in both sexes, in 1970. Those below 6 years are free from infection. Prevalence is low in the younger age groups (6-10 years) but rises in the age groups of 16 years and above to 12.4% in males and 10.6% in females.

It was noticed that most of the infected children came from the Nubian villages neighbouring the former town of Wadi Halfa. The children of the remainder of this town are almost free of infection.

(ii) *Results of stool examination in the Old Halfa district*: The stools of 1009 individuals of both sexes and various age groups were examined for the ova of *S. mansoni* by the direct smear method; 322 individuals (132 below 15 years and 190 above that age consisting of 176 males and 146 females) had their stools examined by the digestion concentration technique. No case of *S. mansoni* was detected.

(iii) *Malacological surveys in Northern Province*: Recently a survey further south in the northern province showed that both *Bulinus truncatus* and *Biom-*

phalaria pfeifferi occur in agricultural pump schemes.

b) *Khashm El Girba area (New Halfa), Eastern Sudan*

(i) *Prevalence of schistosomiasis in the transplanted Nubian population in New Halfa*: It should be noted that the resettlement, although it started in 1964, was drawn out over several years, many families moving in later, or women and children remaining in the old area to join their husbands or parents only after a lapse of 3 or 4 years:

Surveys for schistosomiasis have been made in the new area from 1969 onwards. Since not all of the younger children are born in the area, special attention is paid to those known to have been born in New Halfa.

The prevalence of *S. mansoni*, an infection that was not present in the old Wadi Halfa area, is shown in Table 3.

The prevalence of *S. haematobium* is shown in Table 4. It is generally low. It is highest (8.7%) in males of age group 16 years and above. A follow-up study for

TABLE 3. Prevalence among Nubians in Khashm El Girba of *Schistosoma mansoni* infection, a disease unknown in the old area (1970)

Age in years	Males		Females	
	No. Examined	% Infected	No. Examined	% Infected
0 — 5	432	2	317	1.8
6 — 10	322	6.2	350	3.4
11 — 15	365	8.4	321	8
16 and above	261	8.8	249	8.4

Among young children known to be born in New Halfa, the prevalence of *S. mansoni* infection was 4% in both males and females.

both types of schistosomiasis in the 0-10 year age group in the New Halfa resettlement area is shown in Table 5. A comparison of the percentage distribution of the prevalence of schistosomiasis in the various age groups in Old Halfa and in the New Halfa resettlement area is shown in Table 6.

(ii) *Schistosomiasis among the indigenous population of Eastern Sudan*: A total of 297 individuals, 190 males and 107 females from El Galgala village, between the ages of 6-57 years, had their stools and urines examined by concentra-

tion and centrifugation methods respectively.

The prevalence of *S. mansoni* was 9.6% (29 cases) and of *S. haematobium* 4% (12 cases).

(iii) *Snails of the region*: Table 7 shows the relative frequency of the various snails in the New Halfa area.

D. Western Sudan

As mentioned previously, in the Sudan medical annual report of 1927 schistosomiasis was regarded as being

TABLE 4. Prevalence of *Schistosoma haematobium* infection among Nubians in New Halfa (Khashm el Girba) 1971.

Age group in years	Males			Females		
	No. examined	Infected		No. examined	Infected	
		No.	%		No.	%
0 — 5	437	13	2.9	321	9	2.8
6 — 10	326	17	5.2	354	14	3.9
11 — 15	367	25	6.9	322	18	5.5
16 and above	263	23	8.7	250	15	6
Children born in New Halfa	274	5	1.8	295	7	2.3
Total	1667	83	4.9	1542	63	4.1

TABLE 5. Follow-up stool and urine examination in children under 10 years old in the New Halfa resettlement area (Khashm el Girba), 1969-1973.

Type of schistosome	1969		1971		Dec. 1972 - Jan. 1973	
	No.	%	No.	%	No.	%
<i>S. haematobium</i>	929	5.3	787	6.0	693	3.4
<i>S. mansoni</i>	927	2.9	779	5.5	690	13.2

TABLE 6. Comparison of percentage distribution of schistosomiasis prevalence in the various age groups in Old Halfa and the New Halfa resettlement area (1970-1971).

Age groups (years)	<i>Schistosoma mansoni</i>		<i>Schistosoma haematobium</i>	
	Old Halfa	New Halfa	Old Halfa	New Halfa
	%	%	%	%
0 — 5	0	1.9	0	2.9
6 — 10	0	4.9	2.3	4.5
11 — 15	0	8.4	10.6	6.3
16 + All	0	8.3	11.6	7.4
children born in New Halfa	—	4	—	2.1

TABLE 7. Relative frequency of some aquatic snails in the New Halfa resettlement area (1972).

Species	Relative frequency	Medical and veterinary importance
<i>Bulinus truncatus</i>	abundant	intermediate host of <i>S. haematobium</i>
<i>Bulinus forskalii</i>	common	intermediate host of <i>S. bovis</i> (experimental)
<i>Biomphalaria pfeifferi</i>	abundant	intermediate host of <i>S. mansoni</i>
<i>Lymnaea natalensis</i>	common	intermediate host of <i>Fasciola gigantica</i>
<i>Melanoides tuberculata</i>	abundant	Nil
<i>Cleopatra sp.</i>	abundant	Nil

endemic in some parts of Kordofan and Darfur provinces in the Western Sudan. Later Greany (1952a) in a survey in the Gezira made in 1949 detected both types of schistosomiasis among immigrant tribes coming from Western Sudan. *S. haematobium* infection was slightly more common among them than *S. mansoni*. The ranges of both infections varied between 9.2% and 18% among the

various age groups and sexes. It was generally higher than among the corresponding groups of the indigenous population of the area.

However, it is now accepted that the prevalence of both types of schistosomiasis in Western Sudan is sporadic and variable in the different regions. *S. haematobium* infection is more common. A recent survey by Dr. El Tom, of the

Faculty of Medicine, Khartoum, gave the prevalence of *S. haematobium* infection as varying from 0-100%, the average being 10%. *S. mansoni* infection is present in small foci. Western Sudan is an area where water resources are lacking and thirst threatens people when rainfall is small. The yearly rainfall in this region varies in different years and different regions (340 mm to over 1000). Numerous pools of water (Hafers or Fulas) are filled during the rainy season. The pools retain the water for most of the year. *Bulinus* snails are found in large numbers in these pools (Abdel-Malek, 1958). *Biomphalaria pfeifferi* were found in some parts of Western Sudan in the Jebel Marra area.

E. Southern Sudan

Agriculture in Southern Sudan is mainly by rainfall, which is heavy, and in the southernmost regions occurs in most months of the year. However, collections of water are formed in certain river basins when tributaries cause flooding along the banks. In some areas of Bahr El Ghazal extensive swampy areas are formed. Abdel-Malek (1958) identified the snail vectors in the south as *Bulinus* (*Physopsis*) *globosus*, *Bulinus* (*Physopsis*) *ugandae*, *Biomphalaria sudanica* and *Biomphalaria rüppellii*. Early reports stated that schistosomiasis is endemic in all of the three southern provinces, with a higher prevalence in Equatoria province.

During 1970-71, we saw in Khartoum more than 200 patients coming from Bor area in Southern Sudan. They showed a severe form of *S. mansoni* infection. We treated 95 of them with Etranol in a drug trial (Omer et al., 1972). This large number of patients reporting to Khartoum from such a remote area attracted our attention to an outbreak of the disease in that region, probably resulting from a high flood that had occurred earlier and

had caused flooding of the water on the river banks.

F. Control

1. Control measures so far undertaken in the country

The early observations on the intermediate hosts of schistosomiasis were reported by Greany (1952a), who mentioned that within 3 $\frac{1}{2}$ years of the installation of the canal system in the Gezira irrigated area of the Sudan, snails invaded the whole extent of its 2600 miles. Snail destruction was attempted in the early phases of the Gezira area by the use of copper sulphate in a concentration of 30 ppm. Sacks of copper sulphate were dragged through the water on ropes, in different directions. This system of mollusciciding continued in the Gezira until recently and is still used in the Khashm El Girba area. But often it is not done at regular intervals and does not cover the entire scheme. Sodium pentachlorophenate was also used in the past and this was reported by Sharaf El Din & El Nagar (1955). This molluscicide is not in use now.

Recently the London-Khartoum Bilharzia Research Project selected Frescon (N-tritylmorpholine) for a large scale trial in the Northern part of the Gezira at a dose of 0.075 ppm. The preliminary results of this trial were reported by Amin (1972a). This followed on an assessment of copper sulphate (Amin, 1972b). He concluded that copper sulphate was far from being an ideal molluscicide in the scheme while the application of Frescon at a dose of 0.075 ppm for 30 days resulted in complete coverage of all water courses and the snail populations were kept at a low level for approximately three months.

Niclosamide (Bayluscide) is also on trial on a limited scale. Recently Drs.

Fenwick and Amin of the Gezira Schistosomiasis Research Project used air spraying in mollusciciding (see Fenwick & Amin, 1978). Mechanical traps for snails placed at various parts on the canals were used for a long period in the Gezira. This did not prove to be an efficient way of control and faced some technical difficulties.

Manual removal of weeds from the canals in the Gezira was a common practice for some time, but only on a limited scale. The objective was mainly to increase the velocity of water but the clearance was also helpful in reducing the vegetation on which the snails feed.

Mobile treatment units covered various parts in the Gezira irrigated area, carrying out direct stool and urine examinations and giving treatment to those infected. Unfortunately their method of stool examination missed the majority of bilharzial cases. At the same time, the treatment was generally inadequate as they were using the old antimony drugs, with many patients not finishing their courses.

There was some attempt to use environmental means of control, mainly through the provision of a clean chlorinated water supply in the majority of villages. But generally this ran into some difficulties such as mechanical problems, or lack of petrol, and often the clean water is not brought to taps near to the houses. Families need to go out and collect the water and in such cases they may prefer to use the nearby canal for washing or for other uses.

Very little is done in the way of health education and no effort is made towards proper methods of sewage disposal or provision of proper latrines.

The training given to the personnel involved in schistosomiasis control is

directed at various levels, *e.g.*, to the training of public health officers, of their assistants, of laboratory attendants for mobile units, of technicians and laboratory assistants for the few central laboratories, and of snail collectors.

2. *Results of control measures*

The prevalence data quoted in this paper prove that the previous control methods of schistosomiasis in the Gezira were not efficient. It is perhaps still too early to assess the trials with new molluscicides. Apart from the Gezira and Khashm El Girba area, there are no practical control measures in the country.

3. *Suggested strategy for control measures*

The accepted methods of control of schistosomiasis at the present time are :

- a) snail control by molluscicides and other means.
- b) treatment of cases and mass treatment.
- c) health education.
- d) environmental means of control.

The magnitude of the problem in the various countries concerned and local conditions determine the relative importance of any of those methods, or their combination. As mentioned previously, schistosomiasis is a major public health problem in this country and its prevalence is expected to rise with the expansion in agriculture and in the canal irrigation system. Since, in the Sudan, the spread of infection in various parts of the country is due to different causes and means of irrigation, the best methods of control will differ in the various regions.

In my opinion the simplest and cheapest method of control for all the regions is the provision of a clean, treat-

ed, water supply to the various villages in the agricultural areas. But the clean water should be available all the year round, near all the houses and be adequate for drinking, washing and for having a bath. It is not practical to suggest swimming pools for developing countries with limited resources. However, if the water supply is adequate, the people and especially the children can be advised about the dangers of getting in contact with the canal water.

The second important measure would be the provision of proper deep pit latrines for all the houses, and of public latrines near the places of work. The local councils and the government should contribute to help the poor people. Although it may appear that there is no good reason for these people to defaecate or urinate on the banks of these canals, it is a fact that the habits of the Muslim people to wash after defaecation or urination attracts them to the only available source of water, which is the canal. At the same time the canals' high banks act as shelter for them.

Regarding the use of anti-bilharzial drugs, the writer has been consulted this year by the Sudan Ministry of Health and asked to suggest a scheme to be applied in the years 1977-84 in the Gezira irrigated area. The present results of the prevalence of schistosomiasis in the various age groups and the intensity of infection were shown to the committee. It was therefore suggested to carry out

mass treatment in 1977 in the Gezira for all those between 7 and 15 years old. This age group has an 80% incidence of infection as revealed by one stool examination and hence possibly a true infection rate of 95% or nearly 100%. At the same time, they have the highest intensity of infection and therefore cause maximum transmission. It is always a problem to choose the drug in mass treatment attempts. However, Etrenol was suggested as the drug of choice, because the area is predominantly one of *S. mansoni* infection and Etrenol is given as a one-injection treatment. I suspect that in the future an oral treatment may replace it.

Mass treatment can also play a role in localised foci in the country, e.g., in Western Sudan.

The high cost of molluscicides is a great disadvantage to developing countries as mollusciciding operations need to be repeated regularly. However in large agricultural schemes like those of the Gezira and Khashm El Girba, molluscicides need to be used in launching massive control measures which can be followed or accompanied later by environmental measures.

Another important measure of control in our country is the screening of immigrant labourers and their treatment before being allowed to take jobs in the agricultural projects. It is shown in this study that immigrant labour imported schistosomiasis to agricultural schemes.

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MEASUREMENT OF PHYSICAL PERFORMANCE CAPACITY AND ITS CORRELATION WITH THE ALTERED RATIOS OF REGIONAL BLOOD FLOW IN PORTOPULMONARY AND PORTOSPLENIC SCHISTOSOMIASIS*

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The reduced cerebral blood flow and oxygen carrying capacity of the blood in schistosomiasis and its further reduction during effort induced us to measure the physical performance capacity of affected individuals as compared to healthy individuals.

Twenty patients and 20 controls in the 25-26 year age group were investigated in this study. Patients had a positive history for schistosomiasis for more than 8 years, being positive for either *Schistosoma mansoni* or *S. haematobium*, or both, on parasitological examination. They showed hepatosplenomegaly but no ascites, and had a positive liver biopsy. Portopulmonary cases were diagnosed by clinical examination, radiologic and electrocardiographic findings and by having an elevated central venous picture. The persons investigated were subjected to a progressive exercise test; a bicycle ergometer with an electromagnetic brake was used at increasing submaximal work loads until a «steady state» was reached with regard to oxygen uptake and utilization. A predetermined rate of effort was selected in respect to the size and physical build-up of the individual, to produce

evenly spaced pulse readings over a range of 40-80% of maximum aerobic power relative to this age group.

At first the effect of postural changes on the electrocardiogram was observed. This was followed by continuous recording of the heart rate, blood pressure and analysis of electrocardiographic patterns, before, during and after exertion. Simultaneous multiple quantitative measures of cardiac output by the Khalil Cardiac Thermodilution Catheter were also obtained before, during and after the exercise test.

Results obtained from this study indicate :

1. Considerable reduction of the physical working capacity in all cases affected with schistosomiasis as compared to normal controls. The degree of this reduction depends on not only the stage and gravity of the disease but also on the vascular territories mostly affected. This reduction is considerable in portopulmonary schistosomiasis with a low fixed cardiac output permitting only a limited increase in skeletal muscle perfusion with the required oxygenated arterial blood (Table 1).

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TABLE 1. Means of the physical working capacity in males affected with schistosomiasis, between 25-26 years old.

Data	Normal	Portosplenic schistosomiasis	Portopulmonary schistosomiasis
Mean: Kp/m/min*	898	778	454
Ratio:	1	0.866	0.506
	—	1	0.584

The numerical values are derived, according to Sjostran, from

$$\text{the formula : } \frac{\text{PWC 170 in KP/m/min.**}}{\text{Body surface area}}$$

2. The degree of cerebral oxygen extraction was the same at rest and after effort indicating that it was at its maximum at rest (Table 2).

3. The increased demand for oxygen during effort, with a relatively fixed

cardiac output, subtracts from other regional blood flows that lead to skeletal muscles, stealing it from the cerebral fraction of the cardiac output, as has been shown by the study of cerebral circulation at rest and during effort (Brobeck, 1973).

TABLE 2. Oxygen saturation and degree of cerebral oxygen extraction at rest and after mild exercise. Mean values for portopulmonary cases, 25-26 years old.

State of patient	Time (in min.)	Heart Rate/min.	Oxygen saturation %	
			Arterial blood	Venous blood
Rest	10	74	88	48
Exercise	11	110		
150 Kp/m/min.	12	124		
for 3 min.	13	129		
After effort	16	91	80	40
	17	93		
	19	90		
	22	82		
	24	84		

* Kilo pond/m/min.

** PWC = physical working capacity.

The observations obtained from this study, combined with those concerning the reduced cerebral circulation, particularly during effort, indicate that schistosomiasis not only affects the intellec-

tual functions of sizable masses of the world population but also their physical working capacity. The importance of maintaining these two vital functions cannot be overestimated.

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**MULTIPLE MEASURES OF ALTERED CEREBRAL BLOOD FLOW IN
PORTOPULMONARY AND PORTOSPLENIC SCHISTOSOMIASIS
AT REST AND DURING EFFORT BY TWO NEW
KHALIL THERMODILUTION CATHETERS***

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The present report is part of a study aiming at assessing the impact of schistosomiasis on the intellectual functions and the physical fitness of affected individuals, as well as the resulting socio-economic problems. From a preliminary study in an area near Alexandria, highly endemic for *Schistosoma haematobium*, the author has reason to believe that portopulmonary involvement (cor pulmonale) is relatively frequent in Egypt even when there is no or little *S. mansoni* infection. The effect of pulmonary involvement in cases of varying severity was assessed by multiple measurements of the blood flow in the left internal carotid as an indication of total cerebral blood flow, at rest and during effort, by means of two newly developed Khalil thermodilution catheters. During these measurements, patients were also requested to answer a standard set of simple questions.

**Preliminary Survey in
Deif Village**

A random sample from Deif village 24 km SE of Alexandria representing 22% of a total population of 725, i.e., 160 persons, were examined clinically for

portosplenic and portopulmonary schistosomiasis (cor pulmonale).

Of these 160 cases examined, 60% were found infected with urinary *Schistosoma haematobium* denoting high endemicity and only 4% with *Schistosoma mansoni*. Two cases had combined urinary *S. haematobium* and intestinal *S. mansoni* infection.

The prevalence of the different grades of schistosomal cor pulmonale in this random sample was 6.25%, i.e. 10 cases, nine of which were due to *S. haematobium*. The distribution of the different grades of portopulmonary schistosomiasis (cor pulmonale) was as follows :

- A. 1st grade 1.25%
- B. 2nd grade 3.75%
- C. 3rd grade 1.25%
- D. 4th grade 0.00%

These figures reveal a high prevalence of cor pulmonale in Deif village. We are currently screening neighbouring villages of low, medium and high endemicity to obtain the true ratio of schistosomal cor pulmonale in the area and to assay socio-economic conditions in these villages.

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Materials and Methods

1. Subjects studied

Since the cor pulmonale cases detected in Deif village did not include the most severe stage and were limited in number, other cases of portopulmonary and also portosplenic schistosomiasis were chosen for study from among in-patients at the Alexandria University hospitals, bringing the total of cases investigated to 18.

In the present paper, by way of illustration, data are presented for a selection of five cases of varying schistosomal involvement and severity, one case of early infection with *S. haematobium* being considered as a control (Table 1).

2. Use of thermodilution catheter

To evaluate the total cerebral blood flow in patients with schistosomal cor pulmonale and other schistosomal conditions, 2 newly developed thermodilution catheters were used.

The internal carotid catheter is similar in design and structure to the previously reported Khalil thermodilution cardiac output catheter (Khalil, 1962,

1963, 1968a,b ; Khalil et al., 1966), but different in size and purpose. It consists of an upstream bifilarly wound heating coil, with an outside diameter of 0.8 mm, energized during the 10 seconds of measurement with a high frequency current at 350 k Hz and a downstream bifilarly wound platinum resistance thermometer on the catheter tip of 0.4 mm outer diameter, constituting 1 arm of a 3 lead thermometer bridge, that can measure even transient temperature changes down to 0.001°C.

The jugular thermodilution catheter differs in its design by having the upstream high frequency heating coil at the distal segment and the downstream platinum resistance thermometer on a proximal segment before the vein receives any tributaries.

On applying heat at a predetermined constant rate, a temperature rise reaching a plateau within 3 seconds is recorded from the downstream platinum resistance thermometer (Fig. 1). The degree of temperature rise, which is directly proportional to the rate of heating and inversely proportional to volume flow, ranges between 0.05 and 0.15°C and is obtained from the following formula :

TABLE 1. Patients considered in the present report.

Name	Condition	Infected with
Youssef, A.	Schistosomal cor pulmonale, Grade IV	<i>S. mansoni</i>
Mahmoud, M.	Schistosomal cor pulmonale, Grade III	<i>S. haematobium</i>
Maher, A.G.	Portosplenic schistosomiasis with iron deficiency anaemia	mixed infection
Galal, M.M.	Portosplenic schistosomiasis with ascites	mixed infection
Mahmoud, Z.M.E. (Control)	Early infection	<i>S. haematobium</i>

$$\text{Volume Flow ml/min.} = \frac{W \times 0.239 \times 60}{0.92 \times \Delta T}$$

Where :

W = the predetermined rate of heating in Watts,

0.239 = the conversion factor to calories,

60 = the minute volume,

0.92 = the product of specific heat and density of the blood,

ΔT = the rise of the mean temperature of blood flowing through the carotid artery.

The principle of this method is analogous to that of the continuous dye dilution technique and other conventional methods and is based on identical principles (Hosie, 1962). However, continual measurements of blood flow within a few seconds by this method offer the following advantages :

1) Heat is a naturally occurring indicator in the body and may be compared

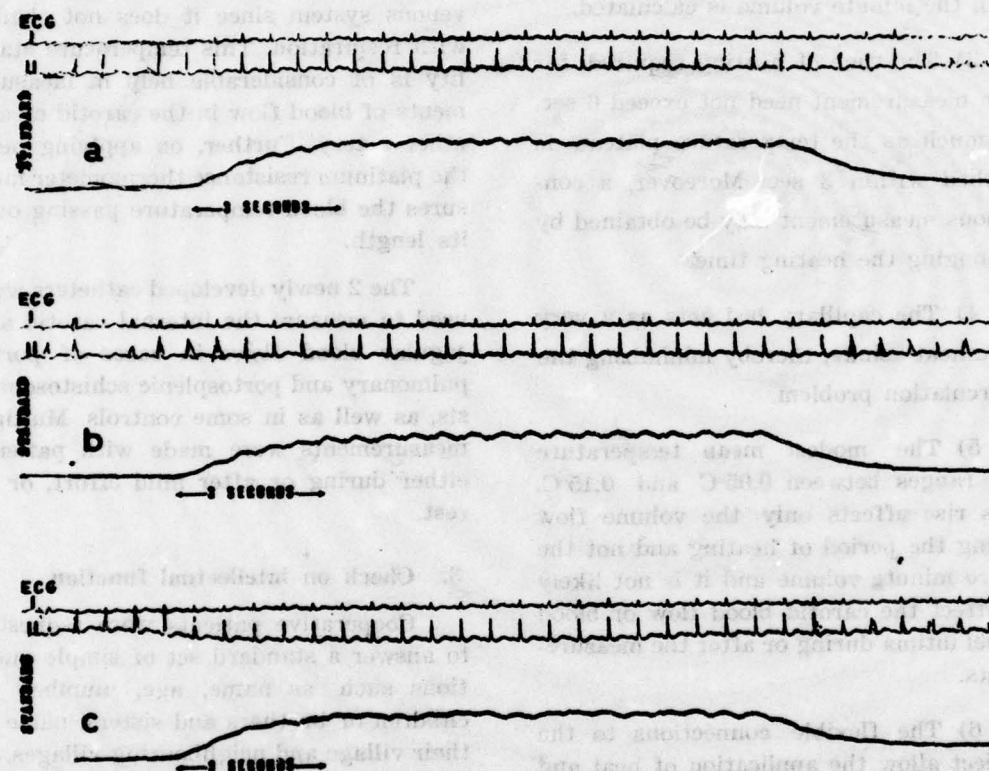


Fig. 1. Internal carotid blood flow measurements by thermodilution in a case of schistosomal cor pulmonale (Grade III). Patient is at rest, in the supine position, with the head in 3 different positions (a, b, c).

Patient's head is facing: (a) up, (b) left and (c) right. Each group of tracings comprises: two electrocardiograms (top rows, bipolar limb leads I and II) and a simultaneous tracing of the blood temperature (bottom row) showing its rise, during the application of heat at a predetermined constant rate, to a plateau within 3 seconds, as recorded by the downstream platinum resistance thermometer. An electrical standardization "Standard" equal to a temperature rise of 0.1°C is recorded before each measurement. The bipolar electrographic leads represent a difference of electrical potential between 2 selected sites:

Lead I = difference of potential between left and right arm.

Lead II = difference of potential between left leg and right arm.

to oxygen as the indicator in the Fick method (Fick, 1870).

2) Each measurement can be carried out without the injection of any substance into the circulation. Other thermodilution studies in man and in small animals require the injection of a volume of saline during each measurement (Forester et al., 1972). This volume is likely to increase the cardiac output during the measuring period, and the error is further amplified when the minute volume is calculated.

3) The time of heating required for each measurement need not exceed 6 sec. inasmuch as the temperature plateau is reached within 3 sec. Moreover, a continuous measurement may be obtained by prolonging the heating time.

4) The capillary bed acts as a very large heat «sink», thereby minimizing the recirculation problem.

5) The modest mean temperature rise ranges between 0.05°C and 0.15°C. This rise affects only the volume flow during the period of heating and not the entire minute volume and it is not likely to affect the carotid blood flow or blood vessel intima during or after the measurements.

6) The flexible connections to the subject allow the application of heat and measurement of temperature rise with ease and without sacrifice of accuracy.

7) It is possible to apply heat and obtain the signal indicative of temperature rise by telemetry.

Contrary to the cardiac thermodilution catheter, the values obtained by the new miniature catheters are independent of blood mixing and laminar flow. This is

because the ratio between the surface area of the heating coil and volume flow is much higher than that in the cardiac catheter. That is, if we used the same ratio in the design of the cardiac thermodilution catheter, we should have a heating coil 100 cm long and a platinum resistance thermometer around 50 cm long, which is not practical.

Blood temperature in the arterial system is far more stable than in the venous system since it does not change with respiration. This temperature stability is of considerable help in measurements of blood flow in the carotid or any other artery. Further, on applying heat, the platinum resistance thermometer measures the blood temperature passing over its length.

The 2 newly developed catheters were used to measure the internal carotid and jugular blood flows in cases of portopulmonary and portosplenic schistosomiasis, as well as in some controls. Multiple measurements were made with patients either during or after mild effort, or at rest.

3. Check on intellectual function

Cooperative patients were requested to answer a standard set of simple questions such as name, age, number of children or brothers and sisters, name of their village and neighbouring villages, as well as counting 2 digits backwards starting from one hundred. This simple test for intellectual functions was compared with that obtained from a similar number of normal subjects of matched age from the same village and under similar socioeconomic conditions.

Results and Discussion

The values obtained from the tracings show :

1. Considerable reduction in mean value of right internal carotid and internal jugular blood flow (I.C.B.F. and I.J.B.F.) in schistosomal cor pulmonale (271 ml/min., with an equivalent value for 100% oxygen carrying capacity of 168 ml/min.) as compared to early schistosomal infection (403.6 ml/min., with an equivalent value for 100% oxygen carrying capacity of 254.4 ml/min.) as illustrated in Tables 2 and 3 and Figs. 2 and 3. This is not evident in portosplenic schistosomiasis associated with anaemia, where the heart and lungs are spared and the blood oxygen carrying capacity is reduced (mean value 350 ml/min. with an equivalent for 100% oxygen carrying capacity of 227.2 ml/min.; Tables 3-5). In both portosplenic and portopulmonary schistosomiasis, the values of blood flow in the internal carotid artery and internal jugular vein, when corrected for the anaemic state and the associated reduction of oxygen carrying capacity of the blood supply to the brain, show a clear indication of cerebral hypoxia. This correlated highly with scores obtained from these patients, when requested to answer our standard set of simple questions. Their degree of alertness, speed of answer and ability to count backwards without mistakes was considerably less than that of their normal controls.
2. The reduced I.C.B.F. and I.J.B.F. in schistosomal cor pulmonale undergoes considerable further reduction during short periods of mild effort on the ergometer at a load of 300 Kpm/min.* (151 ml/min. with an equivalent value

TABLE 2. Repeated measurements by thermodilution of blood flow in right carotid artery of a hospital case* of portopulmonary schistosomiasis mansoni (cor pulmonale, grade IV). Equivalent values of 100% oxygen carrying capacity are given in parentheses.

Posture and state	Time	Mean temp. rise °C	Blood flow (ml/min.)			
			systolic	diastolic	mean	
Supine, at rest	—	0.3435	285	256	271	(168.0)
Supine, during effort:						
300 Kpm/min.	1 min.	0.274	297	272	285	(176.7)
300 Kpm/min.	2 min.	0.298	272	251	262	(162.4)
300 Kpm/min.	3 min.	0.428	186	176	181	(112.2)
300 Kpm/min.	4 min.	0.518	152	149	151	(93.6)
Supine, after effort:						
	1 min.	0.363	225	204	215	(133.3)
	2 min.	0.327	262	218	240	(148.8)
	3 min.	0.375	218	199	209	(129.6)

* Name:	Yousef, A.	Height:	160 cm	Hemoglobin:	62%
Sex:	male	Weight:	62 kg	Hematocrit:	31%
Age:	22 years	Surface area:	1.45 m ²	Prothrombin activity:	60%
				Serum proteins:	4.72g%
				Albumin/globulin:	> 1

* Kp = Kilopond; 1 Kilopond meter = 9.81 Joule; 1 Kilopond meter/min. = 0.1635 Watt.

TABLE 3. Repeated measurements by thermodilution of the blood flow in the right carotid artery in a hospital case* of portosplenic schistosomiasis haematobia (cor pulmonale grade III) under varying conditions. Equivalent values for 100% oxygen carrying capacity are given in parentheses.

Posture and state	Time	Heart rate	Mean temp. rise °C	Blood flow (ml/min.)			Mean
				Systolic	Diastolic		
Supine,	2 min.	93	0.131	308	(939)	277	293 (132)
hyperventilation . . .	3 min.	98	0.146	279	(126)	246	263 (118)
Supine, abdominal compression		98	0.115	351	(158)	311	331 (149)
Supine, Valsalva**	after 30-40 sec.	98	0.183	215	(97)	201	208 (94)
Supine, Isuprel***	during	148	0.123	335	(151)	287	311 (140)
	immed. after	128	0.101	402	(181)	355	379 (170)
	8 min. after	104	0.107	384	(173)	332	358 (161)
	45 min. after	105	0.117	351	(158)	303	327 (147)
Supine, during effort:							
150 Kpm/min.	3 min.	128	0.089	451	(203)	406	429 (193)
300 Kpm/min.	2 min.	135	0.113	251	(158)	323	337 (152)
300 Kpm/min.	4 min.	135	0.115	351	(158)	315	333 (150)
300 Kpm/min.	6 min.	130	0.102	409	(184)	341	375 (169)
600 Kpm/min.	2 min.	135	0.101	423	(190)	341	382 (172)
Supine, after effort	1 min.	120	0.109	409	(184)	307	358 (161)
	3 min.	105	0.146	292	(131)	234	263 (118)
	5 min.	105	0.126	341	(154)	270	306 (138)
	10 min.	102	0.129	336	(151)	264	300 (135)
Supine, head facing:							
up		104	0.095	340	(153)	294	317 (143)
left		102	0.100	320	(144)	283	302 (136)
right		102	0.088	365	(164)	318	342 (154)
up		105	0.087	373	(168)	323	348 (157)
up		105	0.138	286	(129)	267	283 (124)
up		104	0.135	299	(135)	267	283 (127)
left		102	0.130	307	(138)	279	293 (132)
right		100	0.130	307	(138)	279	293 (132)
Standing	immed.	114	0.142	290	(131)	250	270 (122)
	2 min.	112	0.135	295	(133)	269	282 (127)

* Name: Mahmoud, M.
 Sex: Male
 Age: 32 years
 Height: 175 cm
 Weight: 60 kg

Hemoglobin: 45%
 Hematocrit: 21%
 Prothrombin activity: 60%
 Albumin/globulin: > 1

** Valsalva maneuver: forced expiration during closure of epiglottis leading to a decrease in cerebral blood flow. Patient was requested to perform this maneuver for 30-40 sec.

*** Isuprel (Isuprenaline) Beta adrenergic stimulant; this cerebral vasodilator was given as an intravenous infusion of 25 ml in 25% glucose.

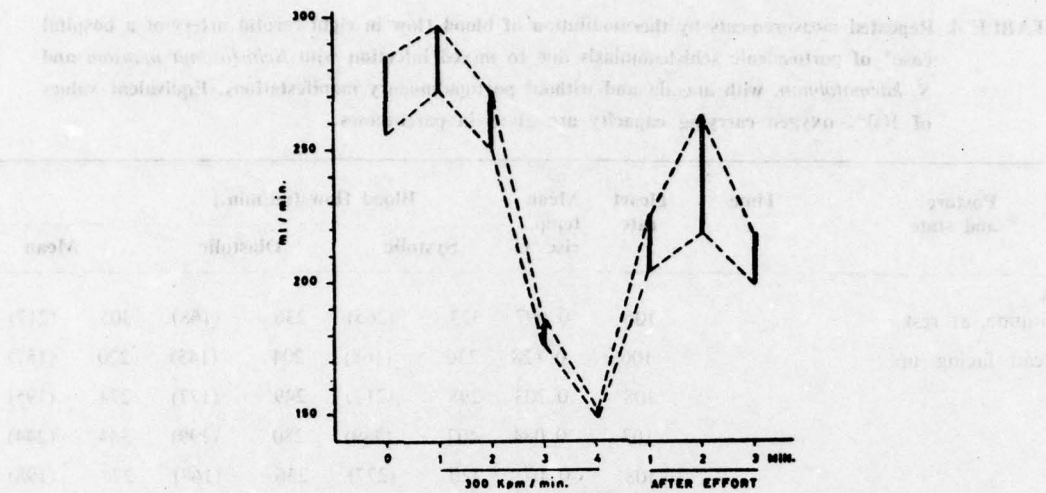


Fig. 2. Effect of mild effort on right internal carotid blood flow (ml/min.) measured by thermodilution in a case of pulmonary schistosomiasis mansoni (cor pulmonale grade IV), (compare with Table 2).

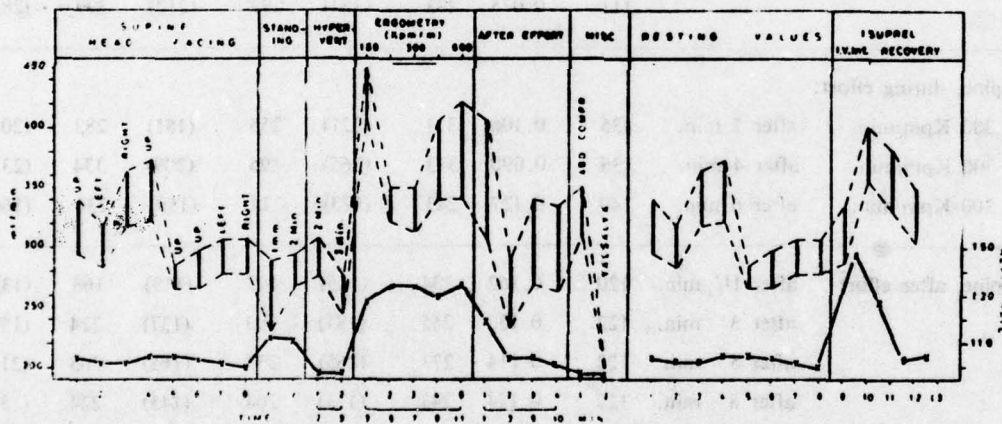


Fig. 3. Effect of various positions, activities and drugs on right internal carotid blood flow (ml/min.) measured by thermodilution in a case of portosplenic schistosomiasis haematobia (cor pulmonale grade III), (compare with Table 3),

- - - - - systolic flow
 diastolic flow
 — X — heart rate

TABLE 4. Repeated measurements by thermodilution of blood flow in right carotid artery of a hospital case* of portosplenic schistosomiasis due to mixed infection with *Schistosoma mansoni* and *S. haematobium*, with anemia and without portopulmonary manifestations. Equivalent values of 100% oxygen carrying capacity are given in parentheses.

Posture and state	Time	Heart rate	Mean temp. rise °C	Blood flow (ml/min.)					
				Systolic		Diastolic		Mean	
Supine, at rest		106	0.097	373	(265)	236	(168)	305	(217)
Head facing up		106	0.128	236	(168)	204	(145)	220	(157)
		108	0.203	298	(212)	249	(177)	274	(195)
		103	0.084	407	(289)	280	(199)	344	(244)
		108	0.103	320	(277)	236	(168)	278	(198)
Sitting		111	0.081	448	(138)	280	(199)	364	(259)
		107	0.081	448	(318)	280	(199)	364	(259)
Standing		110	0.118	263	(187)	213	(151)	238	(169)
		111	0.075	498	(354)	299	(212)	399	(283)
Supine, during effort:									
300 Kpm/min.	after 2 min.	135	0.106	311	(221)	255	(181)	283	(201)
300 Kpm/min.	after 4 min.	136	0.090	373	(265)	295	(209)	334	(237)
300 Kpm/min.	after 6 min.	140	0.127	243	(173)	224	(159)	234	(166)
Supine, after effort	after 1½ min.	120	0.162	204	(145)	167	(119)	168	(132)
	after 3 min.	122	0.135	255	(181)	193	(137)	224	(159)
	after 5 min.	122	0.114	273	(265)	233	(165)	303	(215)
	after 8 min.	122	0.134	243	(173)	204	(145)	224	(159)
	after 10 min.	118	0.096	373	(265)	267	(190)	320	(228)
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* Name:	Maher Abdel Ghaffar		Height:	171 cm		Surface area:	1.76 m ²		
Sex:	Male		Weight:	65 kg		Hemoglobulin:	59%		
Age:	25 years					Hematocrit:	32%		

TABLE 5. Repeated measurements by thermodilution of blood flow in right carotid artery of a hospital case* of portosplenic schistosomiasis due to mixed infection with *Schistosoma mansoni* and *S. haematobium* with mild ascites and anemia, without portopulmonary manifestations. Equivalent values of 100% oxygen carrying capacity are given in parentheses.

Posture and state	Time	Heart rate	Mean temp. rise °C	Mean blood flow (ml/min.)	
Supine, at rest, head facing:					
up		59	0.120	277	(180)
up		61	0.088	376	(244)
left		63	0.080	416	(270)
right		61	0.092	359	(233)
up		62	0.103	322	(209)
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Sitting	immediately	75	0.080	416	(270)
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Standing	immediately	75	0.113	292	(190)
	after 1 min.	74	0.101	329	(214)
	after 3 min.	75	0.103	321	(209)
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Supine, during effort:					
150 Kpm/min.	after 1 min.	89	0.085	392	(255)
150 Kpm/min.	after 2 min.	90	0.095	349	(227)
300 Kpm/min.	after 1 min.	99	0.099	334	(217)
300 Kpm/min.	after 2 min.	107	0.118	282	(183)
450 Kpm/min.	after 1 min.	120	0.124	268	(174)
450 Kpm/min.	after 2 min.	126	0.209	303	(197)
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Supine, after effort	after 1 min.	89	0.111	298	(194)
	after 2 min.	80	0.125	266	(173)
	after 3 min.	82	0.127	261	(170)
	after 5 min.	79	0.128	259	(168)
	after 8 min.	80	0.124	268	(174)
	after 10 min.	81	0.124	268	(174)
<hr/>					
* Name:	Galal Mahmoud Mohamed		Surface area:	1.61 m ²	
Sex:	33 years		Hemoglobin:	65%	
Age:	33 years		Hematocrit:	34%	
Height:	161.5 cm				
Weight:	59 kg				

TABLE 6. Repeated measurements by thermodilution of blood flow in right carotid artery of a case* of early schistosomiasis haematobia without portosplenic or portopulmonary manifestation (control). Equivalent values of 100% oxygen carrying capacity are given in parentheses.

Posture and state	Heart rate	Mean temp. rise °C	Blood flow (ml/min.)					
			Systolic		Diastolic		Mean	
Supine, at rest; head facing:								
up	76	0.087	445	(280)	420	(265)	433	(273)
right	75	0.092	433	(273)	387	(244)	410	(258)
up	75	0.092	421	(265)	404	(254)	412	(260)
left	76	0.097	404	(254)	373	(235)	389	(245)
left	76	0.101	393	(248)	356	(224)	374	(236)
Sitting	86	0.177	227	(143)	202	(127)	214	(135)
	88	0.181	213	(134)	204	(129)	209	(132)
Standing	96	0.181	213	(134)	204	(129)	209	(132)

* Name:	Mahmoud Z. M. Eissa	Surface area:	1.91 m ²
Sex:	Male	Hemoglobulin:	63%
Age:	38 years	Hematocrit:	30%
Height:	178 cm	Prothrombin activity:	50%
Weight:	74 kg	Serum proteins:	3.69 g%

TABLE 7. Oxygen saturation and degree of cerebral oxygen extraction in a hospital case of portopulmonary schistosomiasis (cor pulmonale, grade IV).

State of patient (supine position)	Time	Heart rate	Oxygen saturation	
			Arterial	Venous
At rest	after 10 min.	74	88	48
During mild exercise 150 Kpm/min.	after 1 min.	110		
	after 2 min.	124		
	after 3 min.	129		
After effort	after 3 min.	91	80	40.4
	after 4 min.	93		
	after 6 min.	90		
	after 19 min.	82		
	after 21 min.	84		

for 100% oxygen carrying capacity of 93.6 ml/min.) and returns to its pre-effort level (209 ml/min. with an equivalent value for 100% oxygen carrying capacity of 129.6 ml/min.) within a few minutes. There was no change in the degree of oxygen extraction by the brain during and after effort (Table 7).

3. No significant change in the mean right internal carotid blood flow measurements when the head is facing upwards, to the right or to the left (Fig. 1, Table 3).

I believe that this method for measuring the I.C.B.F. and I.J.B.F. meets most of the requirements of an ideal method for measuring partial and total cerebral blood flow as mentioned in «Progress of Brain Research» (Capon et al., 1968). Furthermore, it is applicable in other accessible vascular territories.

The reduced cerebral blood flow and its further reduction during effort exerts so serious an effect on the intellectual functions and the physical fitness of those affected, that their persistent socio-economic problems should not be underestimated.

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HEPATITIS B ANTIGEN IN BILHARZIAL HBs POSITIVE SUBJECTS INFECTED WITH VIRAL HEPATITIS*

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Both schistosomiasis and viral hepatitis are very prevalent in Egypt. We have previously reported that *Schistosoma haematobium* is an important cause of chronic liver disease in Upper Egypt (Nooman et al., 1974). We have also reported that the carrier rate for hepatitis B (HBs) antigen among our population particularly in rural areas is rather high (Nooman et al., 1973) as in many other subtropical and tropical countries (> 5%).

An experimental study showing that the liver of mice infected with *S. mansoni* offered a particularly favourable bed for the replication of mouse hepatitis virus (Warren et al., 1969), together with the forementioned observations, prompted us to conduct a study of the course of liver disease in «bilharzial» patients infected with acute viral hepatitis (AVH) as compared with that in «non-bilharzial» controls. This report concerns the behaviour of HBs antigen as a marker of hepatitis B infection in both groups of patients.

Material and Methods

The subjects of study were selected from patients newly admitted to Assiut

Fever Hospital with a recent, developing, acute viral hepatitis.

A base-line clinical assessment was made of each patient stressing history of exposure, symptoms and therapy of schistosomiasis, in addition to the data pertinent to the diagnosis of AVH. The laboratory investigations consisted of the following** :

1. Routine urine examination and examination of 24-hr collections of urine for schistosome ova on three consecutive days.
2. Parasitological examination of stools.
3. Examination of rectal snips for schistosome ova.
4. Liver function tests.
5. Liver biopsy : a part was freshly examined for ova and the rest examined histologically.
6. Testing for HBs antigen by counter electrophoresis (Alter et al., 1971).

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** Only investigations related to the present report are here mentioned.

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Except for rectal and liver biopsies, the tests were repeated weekly throughout hospitalization.

Follow-up

Clinical and laboratory evaluation was repeated every three months for the first year and every seven months subsequently.

Results

A total of 204 patients who satisfied the clinical and laboratory criteria for the diagnosis of AVH and who were followed up for periods from six months to two years are the subject of this report (Table 1). A classification of the patients regarding bilharzial infection was based

upon presence or absence of the following criteria :

1. Living and or dead *S. haematobium* ova in urine.
2. Living and or dead *S. haematobium* ova in stools.
3. Ova in rectal snips.
4. Ova in fresh liver biopsy.
5. Histopathological evidence of schistosomal hepatic involvement (granuloma, pigment, portal inflammation and fibrosis).

According to these criteria, the patients fell in two groups : a «bilharzial group» of 93 patients and a non-bilharzial group of 111 patients (Table 2).

TABLE 1. Sex and age of 204 patients with acute viral hepatitis.

No.	Sex	Age in years	
		range	mean
138	Males	4 — 66	24.2
66	Females	2 — 50	20.1
204	M + F	2 — 66	21.6

TABLE 2. Bilharzial and non-bilharzial groups, according to age and sex, in 204 patients with acute viral hepatitis.

Group	Sex	No.	Age in years	
			range	mean
Bilharzial	Males	83	4 — 60	19.9
	Females	10	9 — 25	17.3
	M + F	93	4 — 60	19.7
Non-bilharzial	Males	55	5 — 66	25.7
	Females	56	2 — 50	20.5
	M + F	111	2 — 66	23.1

HBs antigen positive patients

Initial testing of sera for HBs antigen showed that 106, i.e. 52%, of the 204 patients had HBs antigen positive viral hepatitis (Table 3). The corresponding values in the bilharzial and non-bilharzial groups were 44 (47.3%) and 62 (55.8%) respectively. Only the HBs antigen positive patients are considered in the subsequent discussion. It is seen that both the bilharzial and non-bilharzial patients were about equally susceptible to HBs antigen positive hepatitis ($P = 0.25$).

Duration of HBs antigenaemia (Table 4)

Follow-up testing of the HBs antigen positive sera showed that the antigenaemia was detectable constantly or intermittently for periods varying from less than 7 to 550 days (mean 95.16 ± 142.6) in the bilharzial group and from less than 7 to 366 days (mean 35.9 ± 61.2) in the non-bilharzial group. Thus antigenaemia tended to last longer as a whole in bilharzial patients ($P = 0.005$). A breakdown of each group as to duration of antigenaemia shows that 30 from the 62 HBs antigen positive non-bilharzial patients

TABLE 3. Occurrence of HBs antigen in sera of 204 patients with acute viral hepatitis (AVH).

Group	Sex	No. of AVH patients		%
		examined	HBs Ag +	
Bilharzial	Males	83	40	48.2
	Females	10	4	40
	M + F	93	44	47.3*
Non-bilharzial	Males	55	28	50.09
	Females	56	34	60.7
	M + F	111	62	55.8*
Total	Males	138	68	49.3
	Females	66	38	57.7
	M + F	204	106	52

* $P = 0.25$

TABLE 4. Duration of HBs antigenaemia in 106 patients with HBs antigen positive acute viral hepatitis.

Group	No. of patients	Duration in days	
		Range	Mean
Bilharzial	44	< 7 — 550	95.16 ± 142.6
Non-bilharzial	62	< 7 — 366	35.9 ± 61.2

 $P = 0.005$

(48.4%) as compared to 12 from the 44 HBs antigen positive bilharzial cases (27.3%) lost their antigenaemia in less than seven days ($P = 0.025$). At the same time, 9 out of 44 HBs antigen positive bilharzial patients (20.5%) and only three out of 62 HBs antigen positive non-bilharzial patients (4.8%) were chronic carriers for more than six months ($P = 0.01$). The corresponding values for carriers for more than one year are four (9.1%) and one

(1.6%) respectively. The duration of the antigenaemia in those chronic carriers is 210-540 days (mean 344 ± 122) and 180-365 days (mean 241 ± 167) in the bilharzial and non-bilharzial patients respectively ($P = 0.10$) as shown in Table 5.

The nine bilharzial patients who became chronic HBs antigen carriers are described in Table 6. They are predominantly young male patients; seven of them were passing living *S. haematobium* ova in

TABLE 5. Duration of HBs antigenaemia in chronic carriers after AVH.

Patients with HBs Ag Positive AVH	No.	Chronic carriers	P	Duration of prolonged antigenaemia (days)		P
				Range	Mean	
Bilharzial	44	9	0.01	210 — 540	344 ± 122	0.10
Non-bilharzial	62	3		180 — 365	241 ± 167	

TABLE 6. Description of nine bilharzial patients with chronic HBs antigenaemia following acute viral hepatitis.

Sex	Age in years	U.B.	L.B.	Duration (days)			H1	H2
				BH Ag	Trans.	Bilir.		
F	35	+	—	550	180	90	+	+
M	19	—	E	550	90	90	++	++
M	9	+	E	365	270	270	+++	++
M	12	+	+	365	180	90	+++	++++
M	13	+	+	240	90	90	+	++
M	15	+	+	270	210	210	+	+
M	17	+	+	300	28	28	+	+
M	16	+	—	270	90	90	+	++
M	44	—	+	210	90	90	+++	+++

U.B.	=	living schistosome ova in urine
L.B.	=	liver biopsy
—	=	no evidence of bilharziasis
E	=	early bilharziasis
+	=	bilharzial hepatic fibrosis
HB Ag	=	antigenaemia
Trans.	=	transaminasemia
Bilir.	=	bilirubinaemia
H1	=	size of liver on admission
H2	=	size of liver on last observation

their urines when they contracted the illness. Seven had hepatic schistosomiasis and most of them had various degrees of hepatomegaly when they were last examined. There is no strict correlation between the duration of HBs antigenaemia and the activity of viral hepatitis as judged from the duration of the transaminasemia or bilirubinaemia. Unfortunately none of the patients gave his consent for a follow-up liver biopsy.

Relationship of HBs antigenaemia to hepatic schistosomiasis

Liver biopsies were made in 37 of the bilharzial HBs antigen positive patients during the acute stage of illness; of these, 25 patients showed definite histopathological evidence of bilharzial lesions, which was lacking in 12 patients. Within the known limitations of needle biopsy in the diagnosis of hepatic schistosomiasis, the latter can be regarded as non-hepatic bilharzial patients. The mean duration of HBs antigenaemia in the former patients was not significantly different from that in the latter: 81 ± 164 and 113 ± 151 days respectively ($P = 0.25$) (Table 7).

Discussion

Our study shows that when patients already suffering from schistosomal infection are exposed to acute viral hepa-

titis, they are as prone to suffer from disease caused by the hepatitis B virus as non-bilharzial individuals exposed to the same virus. Once infected, however, the bilharzial patient, whether he has bilharzial lesions or not, tends to retain the HBs antigen for quite long periods. These results should be interpreted within the limits of sensitivity of counter electrophoresis as a method for detecting HBs antigen (Wewalka et al., 1973). The technique used in our laboratory, however, detects HBs antigen in all but very weakly positive sera as shown by a multicenter trial to which we contributed (Wewalka et al., 1973). The chance of missing positive cases is offset in this particular study by the frequent testing during hospitalization and in the follow-up period.

The frequency of the carrier rate after an attack of HBs antigen positive AVH is estimated at 5-10% (Mosley, 1975). Incidence is related to: ethnic origin, being more frequent among Mediterranean, subtropical and tropical populations (Prince, 1970); to sex, being more frequent in males; and to age, being more frequent in persons under 30 years of age (Mosley, 1975). All these factors are equally distributed among our bilharzial and non-bilharzial patients which share the same environment, except that non-

TABLE 7. Duration of HBs antigenaemia in 37 bilharzial patients with HBs positive acute viral hepatitis (see text).

No.	Patients	Mean duration in days
	Hepatic bilharzial lesions	
12	absent	81 ± 164
25	present	113 ± 151

$P = 0.25$

bilharzial patients are predominantly city dwellers as contrasted with bilharzial ones, who are predominantly farmers. In a previous study we have shown that the prevalence of HBs antigenaemia among «normal» inhabitants of rural areas in Upper Egypt was 5.7% as contrasted with 1.5% among inhabitants of Assiut city (Nooman et al., 1973). It is well known that bilharzial infection is overwhelmingly more frequent in our rural population than in our urban population. It seems therefore that bilharzial infection predisposes to «retention» of the HBs antigen after the acute attack and that it predisposes to the carrier state. The significance of this observation is twofold. The association of the HBs antigen carrier state with chronic liver disease is almost universally accepted (Nordenfelt et al., 1971). However, we were denied the chance of proving the persistence of hepatitis lesions in the form of chronic aggressive or persistent hepatitis because we were not able to repeat the liver biopsy. The limited data presented in our report concerning the duration of transaminasaemia and bilirubinaemia in chronic carriers do not allow a firm conclusion in that matter.

More apparent is the fact that the persistence of HBs antigenaemia in our bilharzial patients for a long time tends to increase the volume of the reservoir for HB virus in our rural community. Knowing the various parenteral and non-parenteral routes of transmission and excretion of this virus (Sutnick et al., 1970), one can easily imagine the danger of such patients as sources of infection, remembering particularly that they are

excreting virus-loaded blood in their excreta.

The mechanism underlying the persistence of antigenaemia in bilharzial patients is obscure and opens a wide field of speculation. Persistence of antigenaemia has been variously attributed to genetic factors or defects in cell mediated immunity (CMI). No defect in CMI has been detected in bilharzial patients using intradermal testing with streptokinase, streptodornase or phytohemagglutinin (PHA) stimulation of the patients' lymphocytes (Nooman et al., 1978). There is experimental evidence that the livers of mice infected with *S. mansoni* provide a suitable bed for replication of mouse hepatitis virus with increased morbidity and mortality (Warren et al., 1969). The association between bilharzial infection and the persistence of *Salmonella* infection is well known (Hathout et al., 1967). It would go too far, at present, to assume that the worm «carries» the virus; however, we did not find any effect of «successful» specific anti-bilharzial treatment on the persistence of the antigenaemia. Whether the treatment has «eradicated» the parasites, however, is never certain.

Although evidence of impairment of CMI in bilharzial patients was not obtained (in another study; Nooman et al., 1978) by the methods used, one should not exclude the possibility that bilharzial granulomata, composed as they are of multitudes of immunocompetent T and B lymphocytes and macrophages (Warren et al., 1967), might create a relative local defect in the CMI by preventing a sufficiently active defence against the hepatitis virus. Such a defect would not be detectable by the available tests for measuring CMI.

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**NATURAL SCHISTOSOME INFECTION IN RODENTS FROM
ENDEMIC AREAS NEAR CAIRO AND THEIR POSSIBLE
ROLE IN THE TRANSMISSION OF SCHISTOSOMIASIS***

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Few reports have been published on natural rodent infection with human schistosomes in Egypt. The Egyptian gerbil (*Gerbillus g. pyramidum*) was found naturally infected with *Schistosoma mansoni* (Kuntz, 1952) and the Nile grass rat (*Arvicanthis n. niloticus*) with *S. mansoni* and *S. haematobium* (Mansour, 1973a).

The present report presents additional information with respect to this subject.

Materials and Methods

Fifty live traps were set once monthly during the period between June, 1971 and June, 1974 near certain aquatic sites of the irrigation systems in four villages. These villages are : Sindbis in Qualyubiya province, 30 km northwest of Cairo and Mansouriya, Abu Rawash and Kirdasa, Embaba area, Giza province, 30 km west of Cairo. All trapped animals were necropsied within 1-3 days and examined for presence or absence of schistosome worms by perfusion with 0.85% saline of the intrahepatic and extrahepatic portal veins

and the mesenteric veins. Recovered worms were fixed in 10% formalin and stained with carmine and fast green for identification. Livers and intestines of certain positive rodents were digested in trypsin for subsequent egg isolations. A portion of the eggs was hatched in filtered pond water under light and the miracidia were used for infecting *Biomphalaria alexandrina* snails.

Thirty dips with a standard snail collection net were made in each aquatic site near which the traps were set. Snails were collected, counted and examined for natural infection with schistosomes by exposure to light for cercarial shedding.

Results

A total of 52 *Arvicanthis n. niloticus* and 296 *Rattus rattus* were trapped and examined from the four villages (Table 1). Natural *Schistosoma mansoni* infection was detected, in *Arvicanthis*, in 3 of 31 animals from Mansouriya, one of 11 animals from Abu Rawash in *Rattus*, 5 of 64 animals from Sindbis, and 6 of 11 animals from Mansouriya. The rest of the animals (3 *Arvicanthis* and 104 *Rattus* from Kir-

* The opinions and assertions contained herein are the private ones of the author and do not necessarily reflect the official views of the Navy Department, or the naval service at large.

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TABLE 1. Natural infection of rodents with *Schistosoma mansoni*

Village	No. of <i>Arvicanthis</i>		No. of <i>Rattus</i>	
	Examined	Positive	Examined	Positive
Sindbis	7	0	64	5
Mansouriya	31	3*	71	6
Abu Rawash	11	1	57	0
Kirdasa	3	0	104	0
Total	52	4	296	11

* One animal had a mixed infection of *S. mansoni* and *S. haematobium*.

dasa, seven *Arvicanthis* from Sindbis, and 57 *Battus* from Abu Rawash) were negative.

A maximum of nine animals of each rodent species were caught, at any one time, from any of these four localities. Usually not more than two animals were found positive in any collection (Tables 3-6). The majority of infected animals

harbored from two to eight *Schistosoma mansoni* worms (Table 2). However, one *Arvicanthis* from Mansouriya was found to harbor 57 male and 34 female *S. mansoni* worms and one male *S. haematobium* worm. Three *Rattus* from the same area were found to harbor 15 and 9, 14 and 13, 17 and 12, male and female *S. mansoni* worms, respectively.

TABLE 2. *Schistosoma mansoni* worm load in naturally infected rodents

Locality	Host Species	Number Examined	Date Examined	Number Positive	No. of <i>S. mansoni</i> worms		Animal No.
					Males	Females	
Mansouriya	<i>Arvicanthis n. niloticus</i>	1	5/25/71	1	57*	34	523
		3	8/25/71	1	3	2	636
		1	3/16/72	1	4	2	824
	<i>Rattus rattus</i>	6	3/19/73	1	2	2	1356
		9	6/21/73	1	2	2	1501
		3	8/07/73	1	17	12	1589
		3	9/19/73	1	2	3	1675
		1	2/19/74	1	2	2	1864
		5	6/19/74	1	14	13	2001
		4	8/01/72	1	15	9	993
	<i>Arvicanthis n. niloticus</i>	4	8/01/72	1	15	9	993
		4	10/31/72	1	1	1	1117
Abu Rawash	<i>Arvicanthis n. niloticus</i>	8	8/28/72	2	2	2	1013
		5	9/27/72	2	3	5	1017
		4	10/31/72	1	1	1	1053
Sindbis	<i>Rattus rattus</i>	5	9/27/72	2	3	3	1062
		4	10/31/72	1	1	1	1062
		4	10/31/72	1	1	1	1117

* One worm of which is *S. haematobium*.

TABLE 3. Incidence of Schistosome Infection in Rodents, and Snails, from Shattis

Animal	No. of animals positive for schistosomes/No. of animals examined in the different months of the year												
	Year	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
<i>Rattus rattus</i>	1971												
	1972			0/1	0/2	0/1		0/1	2/8	2/5	1/4		0/4
	1973			0/6	0/4	0/1		0/1	0/3	0/1			0/2
	1974	0/6	0/7	0/1	0/2								0/1
<i>Arvicornis</i>	1971												
	1972						0/4	0/1	0/1				
<i>n. niloticus</i>	1973							0/1					
	1974												
<i>Bulinus</i>	1971												
	1972	0/50	0/4	0/45	0/11	0/7	2/15		0/18	0/2		0/82	
<i>truncatus</i>	1973		0/70	3/62	4/52	0/13	*		0/40		0/5		
	1974												
<i>Biomphalaria</i>	1971												
	1972		0/40	0/275	1/105	7/300	35/1420	130/1520	12/282	0/300			
<i>alexandrina</i>	1973		0/250	0/500	4/1120	0/960	*	2/1300	0/220		0/15	11/1182	
	1974												

* Dead snails

TABLE 4. Incidence of Schistosome Infection in Rodents and Snails, from Abu Rawash

Animal	No. of animals positive for schistosomes/No. of animals examined in the different months of the year												
	Year	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
<i>Rattus rattus</i>	1971									0/2			
	1972						0/1	0/2		0/1	0/5	0/2	0/1
	1973	0/3		0/2	0/1	0/9	0/7	0/1	0/4	0/1		0/1	0/1
	1974	0/1		0/3			0/3						
<i>Arvicantis</i>	1971												
	1972			0/3	0/3				1/4				
	1973												
	1974						0/1						
<i>Bulinus truncatus</i>	1971		0/ 50	0/395	0/ 120	0/120	0/125	0/7			dry	6/508	0/84
	1972			0/710	0/1255	0/620	0/ 70			0/2	0/ 88	0/ 35	0/10
	1973		0/600		6/ 387	0/140	0/440	0/275	0/650		0/887	0/100	0/28
	1974												
<i>Biomphalaria alexandrina</i>	1971		0/175	0/1970	0/400	0/930	5/ 350	0/ 10	6/120	0/ 98	dry	38/1520	0/ 786
	1972			0/ 210	0/400	4/505	3/ 200	5/860		2/835	0/630	2/340	0/1600
	1973	0/49	0/798	4/340	4/2480	0/580	3/1440	5/250	1/434		0/720	0/1355	
	1974												

TABLE 5. Incidence of Schistosome infection in Rodents and Snails from Mansouriyah

Animal	No. of animals positive for schistosomes/No. of animals examined in the different months of the year												
	Year	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
<i>Rattus rattus</i>	1971						0/4			0/4	0/5		
	1972			0/4						0/1	0/1	0/3	0/4
	1973	0/5	0/1	1/6		0/1	1/9	0/1	1/3	1/3			0/1
	1974	0/1	1/1	0/3	0/5		1/5						
<i>Arviculthis</i>	1971					1/1	0/4	0/10	1/3	0/1	0/1		
	1972			1/2						0/4			
	1973		0/1				0/1	0/2					
	1974	0/2						0/1					
<i>Bullinus</i>	1971		0/21				0/4						
	1972												
	1973				0/90		0/71	0/35	0/90				
	1974												
<i>truncatus</i>	1971												
	1972												
	1973												
	1974												
<i>Biomphalaria</i>	1971		0/375		2/2845	2/1277	9/950	5/1100	25/3280	0/914	0/320		
	1972			0/360						0/36	0/360	0/165	0/87
	1973	0/640	0/546		9/110	0/148	5/380	40/318	0/89	8/240		0/15	0/268
	1974												
<i>alexandrina</i>	1971												
	1972												
	1973												
	1974												

TABLE 6. Incidence of Schistosome Infection in Rodents, and Snails, from Kirdasa

Animal	No. of animals positive for schistosomes/No. of animals examined in the different months of the year												
	Year	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
<i>Rattus rattus</i>	1971						0/13		0/10	0/4		0/7	0/6
	1972	0/3							0/7		0/3	0/2	0/3
	1973	0/2	0/3	0/7	0/9	0/2	0/6	0/2	0/1	0/2	0/2		0/3
	1974	0/1	0/1	0/5	0/1								
<i>Arvicanthis n. niloticus</i>	1971						0/2		0/1				
	1972												
	1973												
	1974												
<i>Bulinus truncatus</i>	1971	0/202	0/ 20	0/ 9		0/3	0/4				0/1	0/2	0/240
	1972	0/ 75					0/140		0/1	dead*	0/1		
	1973	0/ 45	0/150	0/45	0/25	0/3	0/30		0/5	0/10	dead*		
	1974												
<i>Biomphalaria alexandrina</i>	1971	0/ 393	0/1300	0/1200	0/125	1/3309	43/1415		0/2020	12/1350	0/ 60	9/2055	4/1611
	1972	0/2850					0/ 175	0/1100	43/1800	dead*	40/1700	0/1275	0/1950
	1973	0/6120	0/ 500	0/2300	0/200	0/1200	3/2250	15/ 840	20/ 800	2/ 180	2/ 390		0/ 194
	1974	0/ 468											

* Canals were treated with molluscicides. No collection was made

Infection was detected in *Arvicanthis* during the period between March and August and in *Rattus* between February and October (Tables 3-6). Only ten *Arvicanthis* were caught during the period between September and February and all were negative, but no *Rattus* were trapped during the period between November and January.

On the other hand, *S. mansoni* cercariae were detected in *Biomphalaria alexandrina* snails (collected at the sites where these rodents were captured) during the whole year except in January and February while *S. haematobium* cercariae were detected in *Bulinus truncatus* during April and November in Abu Rawash and during March, April and June in Sindbis (Tables 3-6). The numbers of both species of snails collected during the rest of the year were very small.

In *Arvicanthis*, the male and female *S. mansoni* worms and the male *S. haematobium* worm were normal in size and morphology. Female *S. mansoni* worms were mature, each containing one egg with a lateral spine. The number of testes was 6 to 9 in male *S. mansoni* worms and four in the male *S. haematobium* worm. This strain of *S. mansoni* has been maintained in the laboratory in *Arvicanthis* and laboratory bred *Biomphalaria alexandrina* snails.

In *Rattus* on the other hand, the majority of the worms were stunted and immature. Ova were seen in a few female *S. mansoni* worms and the number of testes was 5 in the majority and 6 or 7 in very few *S. mansoni* males. When infection was passed in normal *Rattus* using laboratory bred *Biomphalaria alexandrina* snails as the intermediate host, more stunted worms than normal ones were

recovered from the same animal after 76 and 78 days of infection.

Discussion and Conclusions

Results indicate the presence of natural schistosome infection in local wild rodents, i.e. with *Schistosoma mansoni*, *Arvicanthis n. niloticus* and *Rattus rattus* and with *Schistosoma haematobium* in *Arvicanthis n. niloticus*. These rodents were caught in areas endemic for human schistosomiasis near aquatic sites where both snail vectors (*Biomphalaria alexandrina* and *Bulinus truncatus*) were found shedding cercariae most of the year.

Rattus rattus spends little time near the water in comparison to *Arvicanthis*. In experimental infections, the yield of worms is low; few worms reach maturity, few eggs are produced and passed in the feces, while infection is self-limiting and may disappear entirely 20 weeks after entry into the body (Kuntz & Malakatis, 1955). Natural infections revealed similar results. Therefore this animal can be considered as a dead end infection.

On the other hand, *Arvicanthis* is widely distributed and lives in burrows on or near the banks of canals and irrigation systems. The heavy worm load and the excretion of viable eggs by this animal in experimental (Kuntz & Malakatis, 1955) and natural (Mansour, 1973b) infections suggest that it can serve as a natural reservoir host. Its habits allow contamination of the water and transmission of infection to snails.

The number of snails and rodents collected during certain periods of the year (Tables 3-6) were too small to exclude presence of infection at that specific time of the year. Therefore, it is difficult to draw a general pattern for the periodicity of their infection.

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PROCEEDINGS OF THE INTERNATIONAL CONFERENCE ON SCHISTOSOMIASIS --ETC(U)

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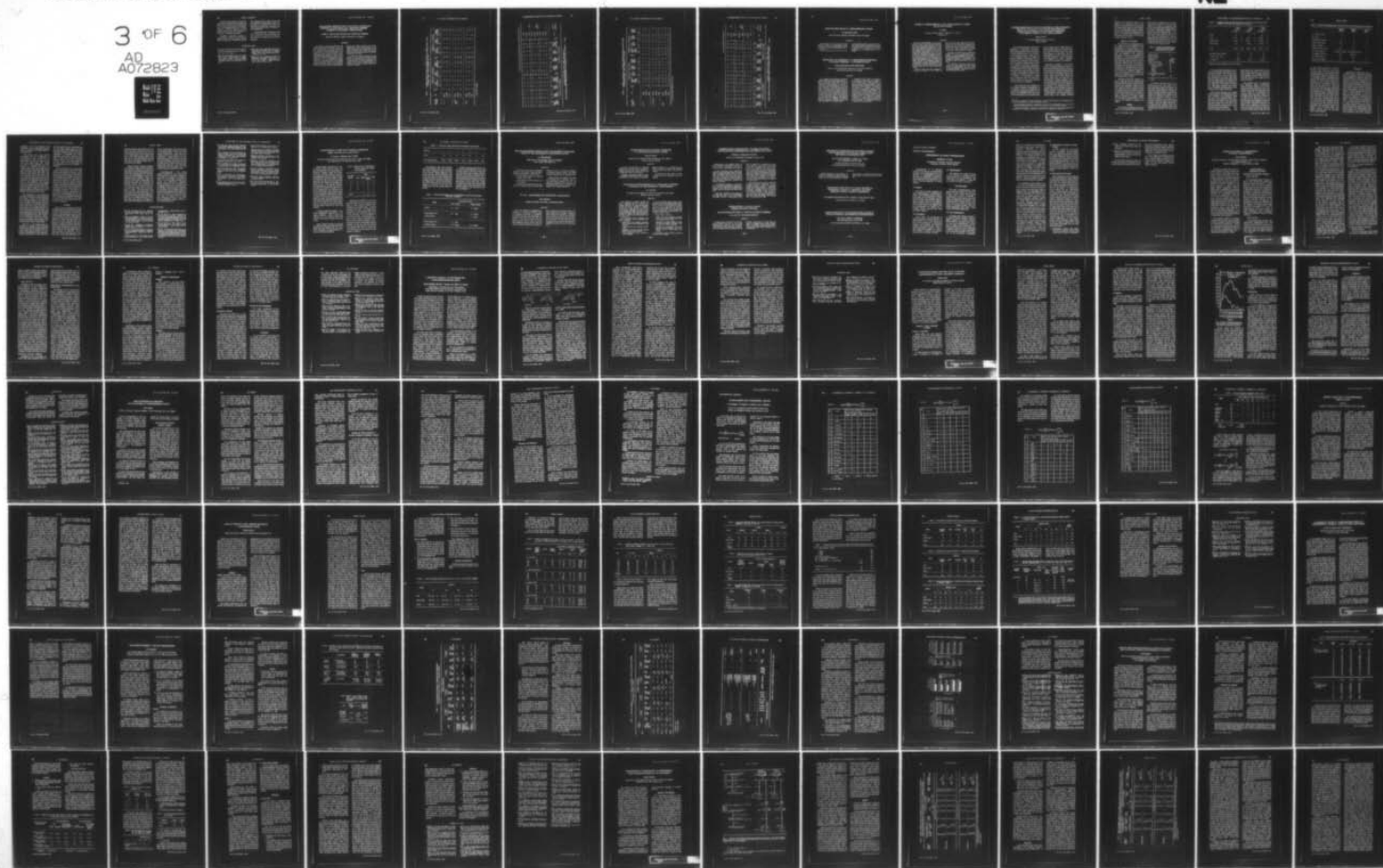
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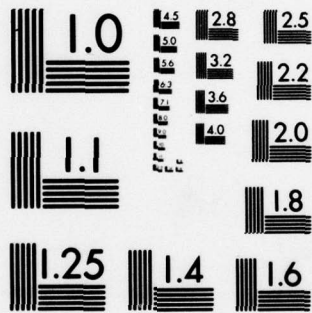
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The low natural incidence of infection and their low intensities may suggest that these rodents cannot play an important role in the epidemiology of the disease. However, sufficient numbers of these animals have not yet been examined to allow for a definitive conclusion.

Therefore, systematic surveys in these areas as well as in other areas in Egypt taking into consideration popula-

tion densities of these rodents in the field and supported by laboratory studies are necessary to determine the exact role these rodents might play in schistosomiasis transmission.

Acknowledgement : The author would like to thank Mr. Fawzy El-Sheikh and Miss Gladys N. Sayegh for their technical assistance.

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**RELATIONSHIP BETWEEN PURE *SCHISTOSOMA HAEMATOBIIUM*
INFECTION IN UPPER EGYPT AND IRRIGATION SYSTEMS :
PATTERN OF BILHARZIAL COMPLICATIONS**

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ABSTRACT

The pattern of bilharzial complications was studied among the rural population of four villages in Upper Egypt, of which one is still under basin irrigation and the other three under perennial irrigation for periods ranging from 3 to 95 years (see Tables). In general, higher rates of hepatosplenic enlargement were found in passers of *Schistosoma haematobium* ova than in non-passers, which emphasizes the association of this complication with *S. haematobium* infection, which thus is not a special feature of *S. mansoni* infection, as is usually believed. The percentage of hepatomegaly was, however, not significantly higher in Garf Serhan, where perennial irrigation has been in use for almost a century, perhaps

because many might be suffering from chronic bilharziasis in which fibrosis prevents the discharge of eggs. The rate of hepatosplenic complications was higher in this village than in Nazza Karar (with only 3 years of perennial irrigation) for both those positive and negative for *S. haematobium* eggs in the urine.

In all villages studied the 0-14 year age group passing ova in the urine and significantly higher rates of liver enlargement than the group aged 15 years and above. This may be attributed to the common occurrence of hepatic enlargement during the invasive stage of bilharzial infection as compared to the later occurring hepatosplenic phase of the disease.

TABLE 1. Frequency of signs due to bilharzial complications among the population studied in Gezirat El-Masabha village,* Assiut Governorate, in 1970.

Age group in years	Sex	Positive for <i>S. haematobium</i>						Negative for <i>S. haematobium</i>							
		No. ex.	Liver enlargement	Spleen enlargement		Hepato- splenomegaly		No. ex.	Liver enlargement	Spleen enlargement		Hepato- splenomegaly			
				No.	%	No.	%			No.	%	No.	%	No.	%
0 — 14	Males	17	1	5.9	0	0.0	2	11.8	441	10	2.0	2	0.5	3	0.7
	Females	1	0	0.0	0	0.0	0	0.0	396	3	0.8	0	0.0	2	0.5
	Total	18	1	5.6	0	0.0	2	11.1	837	13	1.6	2	0.2	5	0.6
15 and above	Males	37	2	5.4	0	0.0	0	0.0	584	28	4.8	5	0.9	12	2.1
	Females	2	0	0.0	0	0.0	0	0.0	454	5	1.1	2	0.4	3	0.7
	Total	39	2	5.1	0	0.0	0	0.0	1038	33	3.2	7	0.7	15	1.4
Total	Males	54	3	5.6	2	3.7	2	3.7	1025	38	3.7	7	0.7	15	1.5
	Females	3	0	0.0	0	0.0	0	0.0	850	8	0.9	2	0.2	5	0.6
	Total	57	3	5.3	2	3.5	2	3.5	1875	46	2.5	9	0.5	20	1.1

* Under basin irrigation

TABLE 2. Frequency of signs and symptoms due to bilharzial complications among the population studied in Nazza Karar village,* Assiut Governorate, in 1968-1970.

Age group in years	Sex	No. ex.	Positive for <i>S. haematobium</i>					Negative for <i>S. haematobium</i>				
			Haematuria and/or dysuria		Liver enlarge- ment		Spleen enlarge- ment		Hepato- spleno- megaly		No. ex.	
			No.	%	No.	%	No.	%	No.	%	No.	%
0-14	Males	383	100	26.1	38	0.9	9	2.3	13	3.4	392	10
	Females	197	17	8.6	10	5.1	0	0.0	4	2.0	479	2
	Total	580	117	20.2	48	8.3	9	1.6	17	2.9	871	12
15 and above	Males	376	54	13.4	1	0.3	4	1.1	0	0.0	517	11
	Females	166	12	7.2	1	0.6	1	0.6	1	0.6	1002	7
	Total	578	66	11.4	2	0.3	5	0.9	1	0.2	1519	18
Total	Males	759	154	20.3	39	5.1	13	1.7	13	1.7	909	21
	Females	363	29	8.0	11	3.0	1	0.3	5	1.4	1481	9
	Total	1122	183	16.3	50	4.5	14	1.2	18	1.6	2390	30

* Converted from basin to perennial irrigation three years prior to survey.

TABLE 3. — Frequency of symptoms due to bilharzial complications among the population studied in El-Ghorayeb village*, Assiut Governorate, in 1968-1970.

Age group in years	Sex	Positive for <i>S. haematobium</i>						Negative for <i>S. haematobium</i>					
		No. ex.	Haemat- uria and/or dysuria	Liver enlarge- ment	Spleen enlarge- ment	Hepato- spleno- megaly	No. ex.	Haemat- uria and/or dysuria	Liver enlarge- ment	Spleen enlarge- ment	Hepato- spleno- megaly	No.	%
0-14	Males	61	35 55.7	9 14.8	3 4.9	7 11.5	44	4 9.1	2 4.5	0 0.0	1 2.3		
	Females	46	22 47.8	7 15.2	2 4.3	3 6.3	51	2 3.9	2 3.9	0 0.0	0 0.0		
	Total	107	57 53.3	16 15.0	5 4.7	10 9.3	95	6 6.3	4 4.2	0 0.0	1 1.1		
15 and above	Males	82	32 39.0	3 3.7	5 6.1	10 12.2	54	13 24.1	1 1.9	0 0.0	1 1.9		
	Females	48	12 25.0	1 2.0	0 0.0	0 0.0	127	21 16.5	3 2.4	0 0.0	0 0.0		
	Total	130	44 33.8	4 3.1	5 3.8	10 7.7	181	34 18.8	4 2.2	0 0.0	1 0.6		
Total	Males	143	67 46.9	12 8.4	8 5.6	17 11.9	98	17 17.3	3 3.1	0 0.0	2 0.2		
	Females	94	34 36.2	8 8.5	2 2.1	3 3.2	178	23 12.9	5 2.8	0 0.0	0 0.0		
	Total	237	101 42.6	20 8.4	10 4.2	20 8.4	276	40 14.5	8 3.0	0 0.0	2 0.7		

(*) Under perennial irrigation for 24 years.

TABLE 4. Frequency of signs and symptoms due to bilharzial complications among the population studied in Garf Sarrhan village,* in Assiut Governorate, in 1968-1970.

Positive for <i>S. haematobium</i>										Negative for <i>S. haematobium</i>									
Age group in years	Sex	No. ex.	Haematuria and/or dysuria		Liver enlarge- ment		Spleen enlarge- ment		Hepato- spleno- megaly		No. ex.	Haematuria and/or dysuria		Liver enlarge- ment		Spleen enlarge- ment		Hepato- spleno- megaly	
			No.	%	No.	%	No.	%	No.	%		No.	%	No.	%	No.	%	No.	%
0 — 14	Males	42	25	59.5	14	33.3	4	9.5	5	11.9	45	4	8.9	12	26.7	2	4.4	5	11.1
	Females	31	11	35.5	3	9.7	1	3.2	1	3.2	57	4	7.0	4	7.0	1	1.8	1	1.8
	Total	73	36	49.3	17	23.3	5	6.8	6	8.2	102	8	7.8	16	15.7	3	2.9	6	5.9
15 and above	Males	56	25	44.6	4	7.1	6	10.7	17	30.4	64	10	15.6	4	6.3	3	4.7	7	10.9
	Females	41	8	19.5	1	2.4	2	4.9	1	2.4	101	4	4.0	3	3.0	2	2.0	0	0.0
	Total	97	33	34.0	5	5.2	8	8.2	18	18.6	165	14	8.5	7	4.2	5	3.0	7	4.2
Total	Males	98	50	51.1	18	18.4	10	10.2	22	22.4	109	14	12.8	16	14.7	5	4.6	12	11.
	Females	72	19	26.4	4	5.6	3	4.2	2	2.8	158	8	5.1	7	4.4	3	1.9	1	0.6
	Total	170	69	40.6	22	12.9	13	7.6	24	14.1	267	22	8.2	23	8.6	8	3.0	13	4.9

* Under perennial irrigation for 95 years.

SOCIO-ECONOMIC IMPACT OF SCHISTOSOMIASIS IN EGYPT

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ABSTRACT

Schistosomiasis ranks first among the health problems in Egypt. Its socio-economic impact, although not yet accurately assessed quantitatively, is well perceived both on the individual and national level.

Almost all figures given as economic loss due

to schistosomiasis in Egypt are merely theoretical ones, and only represent a potential loss as a result of under-employment in rural areas and disguised unemployment. The cost-benefit and cost effectiveness analyses are discussed relative to control projects.

PREVALENCE AND MORBIDITY OF SCHISTOSOMIASIS HEMATOBIA IN EGYPTIAN CHILDREN : A CONTROLLED STUDY

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ABSTRACT

The prevalence and morbidity of schistosomiasis hematobia was studied in three different villages in Giza governorate in Egypt. The survey included 786 children ranging in age from six months to 10 years and grouped in three age periods. There was a marked variation in the prevalence of infection in the three areas, which correlated to the socio-economic standard and sanitary habits. The youngest age of infection was seen in a boy, 14 months old, while the peaks of prevalence were found at the ages of eight and 10 years. The intensity of infection, as indicated by the heaviness of urinary egg output (mean of three successive days) was found to be unrelated to the degree of prevalence in the area concerned. On the other hand, the intensity of infection correlated well with the severity of the clinical picture.

Immediate skin-test reactivity was related to the intensity of infection, but was unreliable as a single diagnostic tool in children. Delayed reactivity was less sensitive. Stool examination for other helminthic infections revealed a greater prevalence in children infected with schistosomiasis than in those not so infected. The impact of schistosomiasis on the general health of children, as shown by anthropometric measurements, was mild, except in heavily infected children, where it was significant. The study focused on the overshadowed young age period, where infection can be radically cured and even easily avoided. The data presented point to the importance of considering the intensity of infection and not its prevalence in weighing the needs for therapy against its toxic effects in children, or in discussing the priorities of treatment in an endemic area.

STUDIES ON SCHISTOSOMIASIS IN THE ARAB REPUBLIC OF YEMEN AND IN SAUDI ARABIA

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ABSTRACT

Studies on schistosomiasis in the Arab Republic of Yemen were conducted during March and April of 1971. During this period, 1,302 urine and 397 stool samples from inhabitants of various areas (mostly rural) were examined, and 137 water bodies were searched for snails. Results indicate the occurrence in most localities of both urinary and intestinal schistosomiasis, with a patchy distribution and various infection rates. The highest prevalence of *Schistosoma haematobium* infection, reaching 100%, was found in villages in the south. Snail intermediate hosts of both schistosomes were found in many habitats in five of the six provinces visited, and experimental studies showed the local *Bulinus truncatus* and *Biomphalaria pfeifferi* to be susceptible to infection with *Schistosoma haematobium* and *S. mansoni*, respectively. It is estimated that more than one million people in Yemen may be infected with one or both of these schistosomes.

Studies in Saudi Arabia were undertaken in November and December of 1974. During this

period, urine and stool samples from the inhabitants of various (mostly rural) areas were examined and 97 water bodies in 46 localities were searched for snails. The results indicate the occurrence of both urinary and intestinal schistosomiasis with a patchy distribution and varying infection rates in most parts of the country.

The snail intermediate host of *Schistosoma mansoni* was found to be *Biomphalaria arabica*. However, for *S. haematobium*, three species of snails, namely *Bulinus truncatus* and *B. beccarii* in the west and *B. wrighti* in the northeast, may transmit the infection; the susceptibility of the two former species has been proven in the laboratory.

The limitation in the size of snail habitats, which consist of wells, small canals, cisterns, small swamps, interrupted streams and ponds, creates special types of transmission, which can be defined as «oasis transmission». This renders control of the disease simple and practical.

FURTHER OBSERVATIONS ON THE DEVELOPMENT OF THE INDONESIAN STRAIN OF *SCHISTOSOMA JAPONICUM* IN WHITE MICE AND PRELIMINARY STUDIES ON THE INDONESIAN, PHILIPPINE AND FORMOSAN STRAINS IN THE TAIWAN MONKEY*

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The Oriental blood fluke, *Schistosoma japonicum*, is distributed throughout widely dispersed areas of Asia and reports of human infections have been documented from Mainland China, Japan, several of the Philippine Islands, the island of Sulawesi (Celebes) in Indonesia and to a lesser extent in Thailand, Laos and Cambodia. In addition, eggs similar to those of *S. japonicum* have been reported at autopsy from an aborigine in West Malaysia (Murugasu and Por, 1973) and adult worms have been reported from a monkey in Sabah, East Malaysia (Kuntz, 1974). Although the parasite is known to occur on Taiwan, no indigenously acquired human infections have ever been documented and the strain has been classified as «non-human» or «zoophilic».

A great deal has been published on the unusual biological characteristics of *S. japonicum* and the accumulation of data from susceptibility studies in intermediate and definitive hosts offers evidence of the existence of an Oriental schis-

tosome complex (Kuntz, 1955). Moreover, recent findings that only humans and dogs serve as definitive host for the Mekong strain of *S. japonicum* and that *Lithoglyphopsis aperta*, rather than *Oncomelania hupensis*, is the intermediate host (Sornmani et al., 1973; Schneider et al., 1975) has added to the dilemma.

Although *S. japonicum* in the Lindu Valley of Central Sulawesi was first reported in 1937 (Brug and Tesh), little was known about the biological characteristics of the parasite until the discovery of the vector snail *Oncomelania hupensis linduensis* (Carney et al., 1973; Davis and Carney, 1973). With the recovery of infected snails it became possible to carry out laboratory studies to determine whether the Indonesian strain of *S. japonicum* was similar to the «classical strains» or possibly had unusual biological or physiological characters as did the zoophilic or Mekong strains. Results of preliminary experiments have been reported elsewhere (Gross, 1975) and evidence presented

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The opinions and assertions contained herein are those of the author and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

The research described in this report involved animals maintained in animal care facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

indicated the Indonesian strain to be similar to the «classical strains» of the parasite. The present report is an account of further basic studies on the development of the Indonesian strain in laboratory mice and on the comparative development of the Indonesian, Philippine and Formosan (Taiwan) strains in the Taiwan monkey, *Macaca cyclopis*.

Materials and Methods

The Indonesian and Philippine strains of *S. japonicum* were established in mice by exposure to cercariae from *O. h. lindoensis* and *O. h. quadrasi* obtained respectively from endemic areas in Indonesia and the Philippines. The Formosan (Chang-hua) strain was established by exposing *O. h. formosana* collected from the Chang-hua area of Taiwan to miracidia from eggs recovered from livers of laboratory infected mice. The respective sub-species of snails were field collected and retained in the laboratory for several months prior to exposure to 3-5 miracidia. The snails were considered negative at the time of exposure since none shed cercariae and sampled specimens were free of cercariae when crushed.

Laboratory mice were exposed to infection with 50 cercariae placed upon shaved abdominal skin in a drop of water. Monkeys were exposed to infection in the same manner with 600 cercariae. Worms were recovered from sacrificed animals by perfusion. Fecal egg counts were made by the Stoll method and the number of eggs in tissue determined by use of the method described by Smithers (1960). The circumoval precipitin (COP) test was done by the method of Yogore et al. (1968).

Results

Ten mice were infected with 50 cercariae of the Indonesian strain of *S. japo-*

nicum and the development of the infection followed (Table 1). Three mice died within a few weeks. The prepatent period for the surviving seven was approximately six weeks. These seven animals had all died by the 8th week and 59% of the worms given were recovered. Egg counts were made prior to death and a range of approximately 400-800 eggs/g feces was determined. The estimated mean number of eggs produced per g of feces per female at the time of autopsy was 46.

TABLE 1. Development of the Indonesian strain of *Schistosoma japonicum* in laboratory mice given 50 cercariae

Number exposed	10
Number survived	7
Prepatent period	6 weeks
Eggs/g feces	400-800
Duration of infection*	7-8 weeks
Total number of worms . . .	205
Percent recovered	59
Immature	18
Males	93
Females	94
Mean Egg/g feces/day/female worm	46

* Death

In another experiment four or five infected mice each were killed at six, seven and eight weeks post-infection to determine the distribution of eggs in the lung, liver, small intestine and large intestine. The egg counts by organ for each animal in the group were pooled and the results are presented in Table 2. At six weeks the majority of the eggs were in the liver and almost as many in the small intestine; only few eggs were found in the lung and large intestine; 65% of the worms given were recovered, with a total of 1055 eggs estimated for each female worm.

TABLE 2. Distribution of eggs of the Indonesia strain of *Schistosoma japonicum* in various organs of mice 6, 7 and 8 weeks after infection with 50 cercariae

	6 Weeks (5 mice)		7 Weeks (4 mice)		8 Weeks (4 mice)	
	No. eggs*	%	No. eggs*	%	No. eggs*	%
Lung	258	< 1	0	0	236	< 1
Liver	28,079	49	68,613	9	90,500	22
Small intestine	23,100	41	643,736	87	256,780	63
Large intestine	5,556	9	27,540	4	59,760	15
Total	56,993	100	739,889	100	407,276	100
Percentage worms recovered	65		66		48	
Total No. ♀ : worms	54		39		29	
No. Eggs/ ♀	1,055		18,971		14,044	

* Egg counts pooled by organ for all mice in the group.

At seven weeks most eggs were found in the small intestine followed by the liver and large intestine; 66% of the worms were recovered and a total of 18,971 eggs was estimated for each female worm. The results at eight weeks were similar with most eggs being found in the small intestine. Only 48% of the worms were found and 14,044 eggs recovered per female worm. The brains of all animals were also examined but no eggs were found.

Four Taiwan monkeys were exposed to 600 cercariae of the Indonesian strain, three monkeys to the Philippine strain and two to the Formosan strain of *S. japonicum*. One monkey given the Philippine strain died and one was killed. Two monkeys infected with cercariae of the Indonesian and one monkey with the Formosan strain were also killed. The remaining four monkeys were permitted to live

until eggs were no longer detected in the stools. Fecal egg counts were made for some animals and the eggs/day/female worm calculated. The COP test was done in all but one case. The results are presented in Table 3.

All monkeys given the Indonesian and Philippine strains demonstrated patent infections while only one of two monkeys given the Formosan strain passed eggs in the stools. The prepatent period was 5-6 weeks for the Indonesian and Philippine strains and eight weeks for the Formosan strain. Eggs were detected in the feces for 17 and 30 weeks in two monkeys given the Indonesian strain and for 15 weeks in one monkey given the Philippine strain. Eggs were found in the feces of one monkey given the Formosan strain for only two weeks and, when the animal was killed several weeks later only

TABLE 3. Development of geographic strains of *Schistosoma japonicum* in Taiwan monkeys given 600 cercariae

	Indonesian strain	Philippine strain	Formosan strain
No. monkeys exposed	4	3	2
No. positive	4	3	1
Prepatent period (weeks)	5-6	5-6	8
Patency period (weeks)	17,30	15	2
Monkeys autopsied	2	2	1
Length of infection (weeks)	20,19	9,14	17
No. worms recovered	83(37 ♀), 119(56 ♀)	105(65 ♀), 192(73 ♀)	2
Fecal eggs/day/ ♀ worm	508	480, 1093	—
No. COP Test/positive	3/3	3/3	0
Week COP Test positive	6-7	7-8	0

two male worms were found. A total of 83 (14%) and 119 (19%) worms were recovered from two monkeys infected with the Indonesian strain and 105 (18%) and 192 (32%) from two monkeys given the Philippine strains. Histological examination of various tissues was made at autopsy. The livers of all monkeys contained eggs of *S. japonicum*, except that given the Formosan strain. Fecal egg counts were carried out on one autopsied monkey given the Indonesian strain and two monkeys given the Philippine strain, the estimated number of eggs per female worm being 508, 480, and 1093, respectively. The COP test was carried out on sera from three monkeys each exposed to the Indonesian and Philippine strains and from two monkeys infected with the Formosan strain. All monkeys given the Indonesian and Philippine strains were positive at six to eight weeks while neither monkey given the Formosan strain became positive.

Discussion

Preliminary results based upon susceptibility studies in laboratory mammals and in geographic strains or sub-species of *Oncomelania hupensis* have shown the Indonesian strain of *S. japonicum* to be similar to the «classical» Philippine, Chinese and Japanese strains of the parasite (Cross, 1975). In these studies all laboratory animals exposed to the Indonesian strain demonstrated infection patterns similar to those reported for other pathogenic or human strains. In the same studies six sub-species of *O. hupensis* were exposed to miracidia of the Indonesian strain. The life cycle was completed in only *O. h. lindoensis*, the natural host, and *O. h. chiu* from Taiwan. *O. h. chiu* is reported susceptible to all known geographic strains of the parasite (Chiu, 1968) except possibly for the Mekong strain which remains to be studied. The other snail sub-species tested and considered

refractory were *O. h. formosana* from Chang-hua, Ilan and Kaohsiung, Taiwan, and *O. h. quadrasi* from Leyte Island in the Philippines.

The present data offer further information on the development of the Indonesian strain in mice and the distribution of eggs in tissues at six, seven and eight weeks. The results are more or less comparable to those reported or reviewed by others involving studies with other human strains of the parasite, (Hsü & Hsü, 1958, 1960, 1968; Ho, 1963; Chiu, 1967, 1968; Fan & Khaw, 1969; Chiu & Kao, 1973; Chiu & Lu, 1969 and 1974). Of interest in the present study is the similarity of egg distribution in the Indonesian strain to that found in the Philippine and Japanese strains as reported by Hsü & Hsü (1960). In all three strains the percentage distribution of eggs is highest for the small intestine, except for animals with the Indonesian strain killed at six weeks.

The development of the Indonesian strain of *S. japonicum* in Taiwan monkeys was similar to that of the Philippine strain. Animals exposed to cercariae from the two strains of the parasite developed patent infections and produced eggs for 15-30 weeks. Two monkeys given the Indonesian strain were killed and 14% and 19% of the worms recovered, while in one monkey that died and one that was killed with the Philippine strain, 18% and 32% of the worms were recovered. Furthermore, all monkeys given these human strains of the parasite demonstrated positive COP tests in six to seven weeks.

Only one of two monkeys given the Formosan or zoophilic strain developed infection. The animal produced eggs for a few weeks and at autopsy two male worms were found. Sera from the positive monkey demonstrated a weak COP test,

but the reaction was not considered positive. The above results support previous findings by Hsü & Hsü (1956, 1958, 1968) showing the Taiwan monkey to be highly susceptible to infections with human pathogenic strains of *S. japonicum* while being a poor host for the Formosan zoophilic strains. This paper constitutes the first report on the development of the Indonesian strain of the parasite in monkeys.

At the present time it is questionable whether the zoophilic strain of *S. japonicum* is still enzootic on Taiwan. During the past several years many thousands of oncomelanids from old and new localities on the island have been examined for schistosome infections, but the parasite has not been found. In addition, a large number of mammals, as well as feces from a variety of animals, have been examined and these have also been negative for schistosome infections. The reasons for the failure to find the parasite are not known but industrialization of the once endemic areas and increasing mechanization of farming practices may have had an impact upon the ecology and consequently transmission.

Summary

White mice were exposed to infection with 50 cercariae of the Indonesian strain of *Schistosoma japonicum*. The prepatent period was approximately six weeks; egg counts ranged from 400 to 800 eggs per gram of feces per day. The animals were autopsied at seven and eight weeks and 59% of the worms recovered. The mean number of eggs produced/g feces/day/female was estimated to be 46. Other mice were infected and killed at six, seven and eight weeks and the egg distribution in various organs was estimated. At six weeks 49% of the total eggs were in the liver, 41% in the small intestine, 9% in

the large intestine and less than 1% in the lungs. At seven weeks 87% were in the small intestine, 9% in the liver and 4% in the large intestine and at eight weeks 63% in the small intestine, 22% in the liver, 15% in the large intestine and less than 1% in the lungs. No eggs were recovered from the brains.

Taiwan monkeys (*Macaca cyclopis*) were exposed to 600 cercariae of either of the Indonesian, Philippine and Formosan (Chang-hua) strains of *Schistosoma japonicum*. All monkeys given the Indonesian strain (four) and Philippine strain (three) developed patent infection; eggs were detected in the feces for 15-30 weeks. Two monkeys each given the Indonesian and Philippine strains were autopsied and 14% and 19% of the worms were recovered from the former and 18% and 32% from the latter. Fecal egg counts were made and 508 eggs/day/female worm were estimated for one monkey given the Indonesian strain and 480 and 1093 eggs/female in two monkeys given the Philippine strain. Sera from the monkeys infected with the Indonesian and Philippine

strains demonstrated circumoval precipitin antibodies (COP) within six to eight weeks post-infection. Only one of two monkeys given the Formosan strain demonstrated a patent infection at eight weeks and eggs were found in the stools for only two weeks; this animal was killed after several weeks and only two male worms were recovered. The circumoval precipitation test was negative for both monkeys given the Formosan strain.

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SUPERINFECTION OF MICE WITH UNISEXUAL CERCARIAE FROM *BIOMPHALARIA ALEXANDRINA*

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Immunological comparisons of male and female worms did not show any essential difference in the distribution of detectable antigens. Male and female worms give the same pattern in immunoelectrophoresis when run with anti-male or anti-female sera from rabbits. Since there does not seem to be any noticeable difference, the induction of immune response, if any at all, during infections with *Schistosoma mansoni*, also must be the same. For studies of infection immunity in Bilharziasis, clear statements can be made when there exists a marker which allows to quantitate separately the effect of a basic infection and an artificial superinfection in one animal. Immunologically indistinguishable male and female worms seem to be a good tool for such studies, since one sex can be used for the first infection and the other sex for the second infection.

To obtain unisexual cercariae, we infected *Biomphalaria alexandrina* with a single miracidium. Table 1 shows the infection rate in a group of 100 snails which we were able to infect at the rate of 8%.

Table 2 shows the yield of cercariae per snail, according to the life span of the snails. We were unable to see any significant differences in infections due to a male or a female miracidium.

TABLE 1. Infection rate of 100 *Biomphalaria alexandrina* snails after exposure to one miracidium.

Days after infection	Snails			
	Alive	infected	Non- infected	dead
32	91	5	86	9
36	83	2	81	3
45	67	1	66	14
Totals		8	66	26

Subcutaneous infection of mice with cercariae of one sex in the control groups shows a rather uniform infection rate, irrespective of whether male or female cercariae were used. The subcutaneous application of 50 cercariae each, after various intervals, led to the development of 9.4-11.5 worms, corresponding to a yield of 20%, which is somewhat below that found in bisexual exposure. Superinfection took place 14 days after the first infection. In this case also, 50 cercariae were applied either from the same snail or from another one. The results are summarized in Table 3.

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TABLE 2. — Life span of positive snails and the total numbers of cercariae shed.

Snail No.	1	2	3	4	5	6	7
Days	55	63	77	78	79	84	98
No of cercariae shed	670,34	70,146	80,003	29,515	100,557	73,002	72,271

Superinfection with male cercariae, after pretreatment with male cercariae, gave about double the worm load found in the controls. When pretreated with female cercariae, the development of male worms was about the same, though only a reduced number of female cercariae had developed. On the other hand, superinfection with female cercariae, after primary exposure to cercariae of the same sex, yielded more than the average number of worms.

Roughly speaking, there did not seem to be any marked difference in the yield of adult worms in the case of pre-infection with either male or female cercariae. However, since there is evidence that a certain degree of immunity can be acquired during infections, it might be that our experiments did not last long enough. The observed increase of the worm burden of female worms, after pretreatment with female cercariae, is presently under intensive investigation.

TABLE 3. Yield in male and female worms after superinfection of 50 mice each with cercariae of the same or opposite sex.

Groups	First infection with 50	
	Male cercariae	Female cercariae
Controls	11.5 males	9.4 females
Second infection with	24.2 males	9.7 females
50 male cercariae		11.3 males
Second infection with	12.3 males	
50 female cercariae	10.4 females	39.7 females

THE FINE STRUCTURE OF THE TEGUMENT AND ELEMENTS ASSOCIATED WITH IT IN THE MIRACIDIUM OF *SCHISTOSOMA MANSONI*

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ABSTRACT

The body wall of the miracidia of *Schistosoma mansoni* has been studied by light and electron microscope. The tegument is characterized by:

- a) cubical epidermal laminae, with a halo and vesicular contents, and
- b) a base membrane laterally connected to the cubic elements.

The muscle stratum lying beneath the tegument layer is made of annular and longitudinal

fibrillae, as well as of numerous mitochondria, an endoplasmic reticulum, lamellar and double membrane structures, spiral or irregular in shape.

Special attention was focused on the structures associated with the tegument; these are cilia, microvilli-like appendices and thin, long appendices amounting to six in number in our test specimens, and finally two types of sensory papillae on the so-called terebratorium.

IN VIVO DEVELOPMENT OF *SCHISTOSOMA HAEMATOBII*

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ABSTRACT

The in vivo development of *Schistosoma haematobium* in the hamster was studied. Six stages of development, characterized by morphological and histochemical criteria, were distinguished. The 1st stage was the «lung form» (nine days post-infection). Gut formation occurred in the 2nd stage «closed gut form» (18 days). In the 3rd stage «organogeny» (24 days) the male and female worms were easily differentiated: one testis was

seen in the male and a very narrow uterus in the female. Mating and the formation of testes containing spermatozoa «gametogeny» characterize stage 4 (38 days). In stage 5 «egg shell formation» (53 days) vitelline follicle cells have developed in the female. The last stage (61-63 days) «oviposition» is characterized by the appearance of well-developed eggs in the uterus of the female worm.

SCHISTOSOMIASIS AND TAPEWORM INFESTATION IN A 3000-YEAR OLD EGYPTIAN MUMMY

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ABSTRACT

An autopsy was performed on a 14-year-old adolescent boy, weaver by trade, who died about 3000 years ago, in ancient Egypt. Although not properly mummified, he was preserved naturally by dessication, with his organs *in situ*.

Histological examination revealed his tissues to be remarkably well preserved. There was marked cirrhosis of the liver associated with numerous

hepatic schistosome ova. In addition the large bowel was loaded with tapeworm eggs, associated with two encysted larval forms in the intercostal muscles.

The significance of these findings in relation to present day parasitic infestation in Egypt was discussed.

UTILIZATION OF WATER RESOURCES IN DEVELOPING COUNTRIES IN RELATION TO THE PROBLEM OF SCHISTOSOMIASIS

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ABSTRACT

The construction of irrigation systems and dams in developing countries is the most important intervention into the existing natural ecological balance in the tropics and subtropics. For the last 20 years, practically all developing countries have become involved in a process of water resources development, and some of them on a large scale and speedy rate. This process is actively supported by some developed countries, including the U.S.S.R. The latter is assisting 15 countries in building dams, artificial lakes, irrigation systems, etc.

The development of water resources in the tropics is proceeding under the following, rather specific conditions:

- epidemiological and ecological information about the areas under development is still unreliable;
- medical services in many countries are insufficient;
- experience in control of the major parasitic diseases in large areas is lacking;
- existing methods and means of disease control are expensive.

Due to insufficient control measures against schistosomiasis in newly developed areas, the prevalence of the disease has been increasing within the last decade in some countries of America, Africa and Asia. The methodology for control and research of schistosomiasis in a new man-made lake and irrigated areas is being developed, but the practical application of new methods is still awaiting the proper solution.

Priority should be given to:

- creation and better utilization of special services and trained personnel dealing with health problems in new areas;
- organization of regular exchange of methodologically comparable information among such services in different countries;
- development of a methodology for long-term prognosis on schistosomiasis (and other diseases), based on a proper system of surveillance.

The scheme of control measures in man-made lake areas will be discussed.

EPIDEMIOLOGICAL INVESTIGATION ON HUMAN AND ANIMAL SCHISTOSOMIASIS IN MEDITERRANEAN AND MIDDLE EAST AREAS

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ABSTRACT

Epidemiological and biological studies on human and animal schistosomiasis have been made at the Institute of Parasitology, University of Rome, for nearly 25 years and are still in progress.

Le Roux and Biocca (1951) experimentally showed that in Sardinia *Schistosoma bovis* is transmitted by *Bulinus truncatus*; Sadun and Biocca (1962) and Pellegrino and Biocca (1962, 1963) observed that human cercarial dermatitis produced by *S. bovis* is responsible for positive intradermal and fluorescent antibody tests with antigens prepared from human schistosomes, creating serious diagnostic difficulties.

A systematical investigation on the distribution of *B. truncatus* in Sardinia by Coluzzi, Nuvole, Orecchia and Paggi (1965) demonstrated the presence of more than 50 foci of animal schistosomiasis generally associated with human dermatitis.

Comparative investigations were carried out in several other countries of the Mediterranean and Middle East areas: a strain of *B. truncatus* from Algeria was bred in the laboratory and a

strain of *Bulinus* sp., morphologically different from *B. truncatus* by the presence of a deep groove in the shell, was isolated in the Yemen, where it seems to be responsible for the local transmission of *S. bovis* (Orecchia, Paggi and Parrinello, 1973). Epidemiological aspects of *S. haematobium* infection in Tunisia and its importance for Italian visitors was studied by De Carneri, Orecchia and Paggi (1970). Recently, Biocca (1974) investigated the distribution of *B. truncatus* in the region of Lake Assad in Syria in connection with the danger of human schistosomiasis spreading in consequence of the big barrage.

These studies have been, and are, associated with several biological investigations on monomiracidial infections of snails and successive monosexual cercarial infections of experimental animals with different species of schistosomes (*S. bovis* and *S. mansoni*) in view of testing the interbreeding possibilities between such species, the development capacity of these parasites in mono- and bisexual infections, and the host-parasite relationship during the infection (Orecchia and Paggi, 1971; Paggi and Orecchia, 1973; Orecchia, Paggi, Di Prete and Fiore, 1973).

DISEASE SURVEY OF PALOLO VALLEY, CENTRAL SULAWESI (CELEBES)

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Work Unit No. MF51.524.009-0030BF61

ABSTRACT

A disease survey of the Palolo Valley was conducted during 1974. The Valley is south of the previously known Indonesian focus of schistosomiasis japonica at Lake Lindu and is drained by a river from Lindu. Only three cases of schistosomiasis were encountered, all individuals who had

travelled to Lake Lindu or to Napu Valley, the only other recognised focus of human schistosomiasis in all Indonesia. Other helminthic diseases, however, were common in Palolo inhabitants. It is concluded that Palolo Valley is presently free of schistosomiasis.

**PRELIMINARY INVESTIGATION OF BILHARZIAL PATIENTS
FOR THE PRESENCE OF AUSTRALIA ANTIGEN USING
THE LATEX AGGLUTINATION TEST**

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ABSTRACT

Bilharzial patients in various stages of the disease with and without a previous history of jaundice were tested for the presence of Australia antigen using the latex agglutination test. Results

were correlated to the clinical stage of the disease, previous history of injection and attacks of jaundice.

**COMPARATIVE FIELD STUDY OF CANCER BLADDER IN
BILHARZIAL PATIENTS IN PERENNIAL AND BASIN
IRRIGATION AREAS IN ASSIUT GOVERNORATE**

A.M. Ibrahim, H.M. Hammam, M.H. Shalaby, S. Atta and M.I. Taha

Assiut Faculty of Medicine, A.R. Egypt.

**HISTOPATHOLOGICAL AND PARASITOLOGICAL STUDIES OF
DOUBLE INFECTION IN EXPERIMENTAL SCHISTOSOMIASIS**

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E.H. El-Raziky and A. Abdel Latif**

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SECOND PLENARY SESSION

Chairman's Opening Remarks :

CHEMOTHERAPY OF HUMAN SCHISTOSOMIASIS

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Chemotherapy is an important method for the control of schistosomiasis especially if it is used together with other measures in well-designed programmes. The uses and limitations of schistosomicidal drugs can best be considered in relation to the three objectives of chemotherapy :

(1) Clinical

The aim is to relieve symptoms and other manifestations of schistosomal infection. The available drugs are particularly useful in the third stage of 'established infection' when clinical manifestations are mainly related to the output of eggs by mature worms. It is less effective in the fourth stage of the disease where the manifestations are largely due to fibrosis, chronic scarring and other irreversible changes.

(2) Pathological

Apart from the improvement in clinical symptoms, another objective of chemotherapy is the arrest and prevention of the progression of pathological changes, and if possible, the reversal of existing pathological damage. Some of these pathological changes, e.g. obstructive uropathy in children, are asymptomatic and are potentially reversible.

(3) Epidemiological

The objective is to reduce and eliminate the reservoir of infection and the contamination of the environment with viable eggs and miracidia. In this way the infection of snails is prevented.

The Ideal Agent

The ideal chemotherapeutic agent should effectively achieve the above objectives, be safe in routine use, be simple to apply and be cheap. Preferably it should retain or even enhance the host's ability to withstand further infection. The limitations of the existing drugs are well-known and do not need to be listed. Certainly, no currently available drug even closely approaches these ideals. Three issues need careful examination :

(1) Toxic manifestations

In keeping with modern concepts of the safety of drugs, candidate schistosomicidal agents are carefully screened. Those which have potential toxic effects for man, show carcinogenicity, mutagenicity or induce other organopathy, are eliminated. There are as yet no universally recognised criteria for the acceptability of drugs and the permissible level of toxicity. In this presentation, **acceptability**

refers to the reaction of the patients to the drug. In other words, what level of unpleasant side-effects, e.g. nausea, vomiting, or painful induration, will they tolerate in order to rid themselves of this infection? No absolute criteria can be established for acceptability but it is in part related to the severity of the disease as perceived by the patients. In other words, where unpleasant or disturbing symptoms accompany the disease, patients may be willing to tolerate significant side-effects from the drug; on the other hand, where the infection is largely asymptomatic or if the symptoms are not regarded as being of serious import by the patients, they are unlikely to tolerate severe side-effects from the treatment.

The permissible level of toxicity refers to the risks of morbidity and mortality associated with the use of the therapeutic agent. Ideally, one should make objective decisions about the permissible level of toxicity by comparing the untreated prognosis with the treated prognosis under various therapeutic regimes, selecting that which appears most favourable to the patient. Although systematic monitoring of drug toxicity makes it possible to compute the morbidity and mortality due to various chemotherapeutic agents, there is very little concrete information about the natural history of these infections in different ecological settings. Certainly in some areas, the infection seems relatively mild, and complications are apparently rare. In other areas however, the intensive infection makes a major contribution to chronic morbidity and mortality in young persons. What then may be a permissible risk in the latter situation may be unacceptable in the former.

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(2) Maximising the benefits of chemotherapy

In order to obtain the best results in terms of clinical and pathological effects, it is desirable to institute therapy at an early stage of the infection and also to prevent re-infection. Maximal benefit to the community is usually best achieved by combining chemotherapy with other control measures, e.g. snail control and improvement of environmental sanitation. The programmes should be strongly supported by health education of the community.

(3) The search for new drugs

Active research for the development of new schistosomicidal drugs continues to engage the attention of research institutes and the pharmaceutical industry. New agents are being investigated with hope of obtaining effective and safe remedies for this disease. It would appear that the effort has been concentrated mainly on finding agents which can kill the worms in man. One could rightly ask whether the three objectives of chemotherapy outlined earlier could be achieved without necessarily killing the worms. Much evidence has accumulated to show that most of the clinical and pathological effects of the mature infection are due to the eggs rather than to the adult worms themselves. The epidemiological aspect is exclusively dependent on the excretion of viable eggs by the host. It would appear therefore that most of the objectives of chemotherapy could be achieved by permanent sterilisation of the parasitic worms without necessarily killing them. If such an agent is discovered it could have several advantages over the schistosomicidal drugs:

- a) Pathological changes and clinical side-effects associated with the dying worms will be reduced or eliminated.

- b) The continuing presence of live worms in the host may retain his premunity.
- c) Selective sterilisation of the parasite may be easier to achieve and may be less disturbing to the host than the killing of the worms.

The search for new agents that can achieve this outcome would depend on the careful study of the reproductive mechan-

isms of the schistosome worms. Modern biomedical techniques should be applied to obtain and refine this information. New approaches to the chemotherapy of schistosomiasis are urgently needed.

Even though this particular example may prove impractical, it illustrates the way in which modern techniques in biomedical sciences should be employed to search for new tools against tropical parasitic diseases.

BENEFITS AND RISKS OF CHEMOTHERAPY IN HUMAN SCHISTOSOMIASIS

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To obtain a benefit there must be a condition capable of being improved and, in the context of the subject I have been asked to discuss, this leads on to the question : what are the deleterious effects of schistosomiasis ? Even now they are debated but the view that they are considerable and warrant treatment is now almost universal. A report from the World Health Organization, however (WHO, 1953) was reluctant to admit that significant harm was produced by schistosomiasis on a community basis and another recent WHO report is still hesitant on this point (WHO, 1972). In the latter report it is stated regarding public health considerations in the use of schistosomicidal drugs that «It may be concluded that in some, if not all, infected populations harm would definitely be done by withholding treatment». It is clear that there is still reluctance to accept the view that all infected populations would benefit from treatment.

The harmful effects of schistosomiasis which treatment may be expected to relieve include not only those brought by *Schistosoma haematobium*, *Schistosoma mansoni* and *Schistosoma japonicum* to individuals and communities but also the part these infected persons play in disseminating infection to others.

Harmful Effects of Schistosomal Infections

Schistosoma haematobium infections

Heavy infections

Of the harmful effects of heavy infection with *Schistosoma haematobium* there is virtually no argument. In such infections there has been widespread documentation of the severe damage done to the genito-urinary tract, including the production of strictures, particularly at the junction of the ureters with the bladder ; the production of ulceration in the bladder with calcium deposition on ulcers, secondary bacterial infection of the genito-urinary tract and ultimately the production of renal failure. There is also the question of carcinomatous change occurring in the bladder as a result of schistosomiasis ; this must be borne in mind particularly when carcinogenic effects of schistosomal drugs are being considered.

Light infections

It is concerning light infections with *Schistosoma haematobium* that most argument occurs. The view has often been expressed that surveys of those infected reveal that most are in good health and that, when light, the infection appears to be benign.

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When the First International Symposium on Bilharziasis was held in Cairo in 1962, I addressed myself to this problem (Woodruff, 1962) and put forward evidence indicating a then unusual and even novel view indicating that the lightest infections with *S. haematobium* could have serious deleterious effects. Individual cases were there quoted in which light and transient exposure had led to serious pathology. One patient in whom the only possible exposure had been during a 6-month stay in Nigeria, had eight years later been shown at the Hospital for Tropical Diseases to have bilaterally dilated and calcified ureters with well-marked polypoid formation in the bladder. Another with a similarly short exposure had a well-marked polyp at the orifice of the left ureter and dilatation of both ureters. Yet another had developed a stricture of a ureter with hydronephrosis and another had been demonstrated to have patulosity of a ureteric orifice with urinary reflux as revealed by a micturating cystogram. These individual cases were supported by experience already reported of 61 patients studied at the hospital (Schofield, 1959) all proved to have *S. haematobium* infection and mostly very light infection; yet among these there were 36 with a history of haematuria, 23 with dysuria, 1 with haemospermia and 1 with anal discharge brought about by a rectal granuloma in which ova of *S. haematobium* were demonstrated. This study was a prelude to intense activity aimed at deciding whether *S. haematobium* infection was, or was not, a cause of significant morbidity on a public health scale. Among such studies that of Forsyth (1969) and his colleagues was outstanding. These studies left little doubt that serious morbidity is indeed caused by the infection.

Such studies underline the fact that in cross sectional surveys carried out at a point in time or during a short period of time only a small percentage of those who are infected will at that time demonstrate untoward results of infection. If however the same group are observed over a prolonged period many more will be shown to develop untoward results.

Less easily recognised complications of schistosomiasis

The amount of antibody produced in response to the continued presence of the antigenic stimulus provided by schistosomes almost certainly produces considerable deleterious effects. Some partial protection against reinfection may be provided by it but the question arises as to whether any of this antibody is deposited in situations within the body in which it produces harm. Mahmoud & Woodruff (1975) investigated this problem as part of a wider series of investigations into sites within the body at which complement containing immune complexes are deposited. It seemed that one of the important sites at which such deposition might occur would be the renal glomerulus. Resort was had to experimental animals and here the difficulty was that heavy infections killed the animal before significant deposition had taken place. By infecting animals with only a very small number of schistosomes however and killing them after as long a period as a year it was shown that significant deposition in the glomeruli took place. Such deposition is likely to be the pathological basis for the nephrotic syndrome which from time to time occurs in humans infected with *S. haematobium*.

Schistosoma mansoni infections

Heavy infections

Here as in the case of heavy infections with *S. haematobium* there is vir-

tually no argument about their harmful effects. There is ample documentation of the liver cirrhosis, oesophageal varices and papillomata of the large bowel which may result from such infections.

Light infections

Morbidity produced by light *S. mansoni* infections is more difficult to establish than in the case of comparable *S. haematobium* infections. Even so, among the Hospital for Tropical Diseases, London, series, only 15 out of 103 cases with *S. mansoni* infections had been symptom-free during their period of infection. 21 had had blood in the stools caused by bowel involvement, including the formation of polyps. Some degree of liver enlargement was detectable in 30, i.e. 29.1% and the spleen was palpable in 12, i.e. 11.6%. Clearly even light infections with *S. mansoni* initiate pathological processes which may become important, particularly if persisting schistosomal infection allows the load of ova to build up in the liver and increase the damage, or if intercurrent disease also adds to liver damage. In this connection Cameron & Gangouly (1964) demonstrated clearly the relationship that exists between the progressive accumulation of schistosomal ova in the liver and the mounting production of fibrosis which they produce. They demonstrated also that this fibrosis is not permanent but may undergo partial or, if mild, even complete resolution when the infection is brought to an end by treatment. This work introduced the concept that, when a patient is suffering from fibrosis or even cirrhosis of the liver due to schistosomiasis, treatment is still worth giving in the expectation that some resolution of fibrosis will then take place.

Schistosoma japonicum infections

Although we are not primarily concerned with these infections here it is

worth noting that the Chinese are in no doubt about the harmful effects that even light infections with this parasite produce. In consequence they are devoting very considerable resources to the control and eradication of *Schistosoma japonicum* infection in their endemic areas.

Harm done by schistosomiasis on a community basis

The damage done by any infection within a community of considerable size is always difficult to assess, an observation which applies not only to schistosomiasis but to onchocerciasis, intestinal helminthic infections and even to malaria. Immense labour is required to collect and to collate carefully sifted information from large numbers of persons. Erfan (1957) in early studies, however, concluded that 70% of hepatic disorders in rural Egypt were schistosomal in origin. Kloetzel (1962; 1967) in Brazil found in a longitudinal survey of patients with chronic schistosomal splenomegaly that 58% of deaths were attributable to *S. mansoni* infections. Barbosa (1969) reported that in a community survey which he carried out 20% of patients who were asymptomatic but who were infected with *S. mansoni* developed clinically recognisable hepatosplenic complications of schistosomiasis during the 6-7 year period of observation. Studies of Forsyth (1969) in East Africa have already been referred to and these show wide spread urinary tract abnormalities resulting from *S. haematobium* infections. Dr. Mahler in his opening address referred to the impairment of individual and community well-being brought about by diseases such as schistosomiasis and of communities being less active than they could otherwise be. There is much evidence of the truth of this concept and many wish that it was easier to quantify and to record this impairment.

In assessing the effect of schistosomiasis in a community it must be remembered that it, like other chronic and slowly developing diseases such as onchocerciasis, produces symptoms and harmful effects which are relatively well-tolerated because they develop so slowly and insiduously. Such diseases are therefore often overlooked and their harmful effect underestimated. They come to form the background of everyday life and though tolerated while causing mild symptoms produce a considerable impairment of health and activity. Often it is not until severe complications occur that the individual takes action and the presence of the disease in the community is noted. In schistosomiasis such complications not uncommonly are severe urinary disorders. A similar situation exists in endemic onchocercal areas where often severe limitation of sight and even blindness and iritis are stoically tolerated as part of the background to everyday life. The fact that these severe disabilities are tolerated however does not justify neglecting them.

Considering all the harmful effects of schistosomiasis it must be concluded that they are great and that in order to obviate them considerable risks would be justifiable. The question therefore arises as to what are these risks? In considering the risks of chemotherapy a general point that should be borne in mind is that in the treatment of persons in hospitals or clinics greater toxicity of a drug can be permitted than is acceptable when the drug is used in the field and particularly when used in the field for mass chemotherapy. When patients are under close observation considerable toxicity may be permissible so long as it is under control. In mass schemes however toxicity even if mild may cause the scheme to

become so unpopular that it will be wrecked.

Benefits of Chemotherapy

Antimony

More experience has been gained with antimony in schistosomiasis than with any other drug and in terms of parasitological cure no drug has surpassed it. It is in respect of toxicity and ease of administration that the newer drugs have advantages. It is sometimes necessary to resist the tendency to think that because something is new it is necessarily better than the old. There have been many classical studies carried out in Egypt on the use of antimony on a mass scale. Work by Abdallah & Moussa (1974) has shown that in their hands antimony is a very good and safe drug. Its administration however needs careful supervision if cardiotoxicity is to be avoided in those who are predisposed to this complication. The less toxic compounds of antimony such as stibocaptate (Astiban) and Bitharcid compare very favourably with most of the drugs currently available and continue to have exciting potential. They are possibly the drugs of choice in patients who have hepatic damage.

Niridazole

This drug has now proved itself to be excellent, especially for the treatment of individual patients. Its use has been followed by high cure rates. After standard dosage, detailed follow-up examinations carried out at least 3 months after treatment and by use of rectal biopsy, stool examination and urine examination, revealed drug failure rates of the order of 5% in *S. mansoni* infections and 1% or less in *S. haematobium* infections (Kanani, Knight & Woodruff, 1970). Some degree of nausea and vomiting are common, in our own series half were affected by one or other of these symptoms and

7% developed a skin rash. Several complications however have been less troublesome than was feared, probably because administration of the drug to those with liver damage has been avoided. Thus, if patients are examined before treatment and kept under supervision during the treatment, excellent results with a high degree of safety can be obtained. The oral administration required is an advantage as far as the labour of administration is concerned but it has the disadvantage that uncooperative persons may not swallow the drug and this could be important in field work. There are obvious advantages in knowing that a drug has been received by a person and parenteral administration is ideal in this respect, provided too many injections are not necessary.

Hycanthone (Etrenol)

This drug has offered one of the most exciting prospects for mass therapy yet known. For treatment of individuals it is less satisfactory in view of the high drug failure rate, estimated at approximately 50% both in *S. mansoni* and *S. haematobium* by Abdallah and his colleagues working in Egypt (WHO, 1972). In this and other reports hepatotoxicity has been the outstanding complication but, as experience has been gained and the optimum dosage settled at 3.0 mg/kg of body weight as a single dose, excellent results have been achieved. From these reports there have, it seems, been 15 deaths in 300,000 persons who have received treatment. This compares with 6 in 200,000 who had received niridazole; a mortality rate in hycanthone of 1 in 20,000 and in niridazole 1 in 33,000. Bearing in mind the lack of selection which there has often been in treating persons on a mass scale and the fact that many of these deaths could now be avoided as a result

of increasing knowledge regarding selection, this is an acceptable mortality rate. The mutagenic and carcinogenic effects of the drug will be discussed in detail later in this symposium but, bearing in mind the serious effects of the disease and the fact it may of itself predispose to development of carcinomata, mass eradication of the disease would appear to be acceptable even if the drug used had some carcinogenic effect. From the published reports it appears highly unlikely that carcinomata resulting from hycanthone treatment would be commoner among those treated than carcinomata ultimately developing as a result of the presence of the disease itself.

Metrifonate and Oxamniquine

The recent introduction of these drugs has added another two compounds to those that would appear to be highly effective and yet possessed of minimal toxicity. They have brought still nearer the dream of being able to offer chemotherapy which, without doing significant harm itself, will obviate the harm done by the disease. More information about these drugs is currently required and much will be provided at this symposium.

Conclusion

It is now possible to state that when the overall risks of chemotherapy in schistosomiasis are looked at, the conclusion appears irresistible that they are not as great as are the risks that are inherent in leaving the disease untreated. There are many drugs that can be safely used for individual patients and with appropriate care most of these can be used on a community basis with great success. The relevant advantages and disadvantages of individual drugs are finely balanced and we can be sure that one of

the many important results of this symposium will be that its members will go away with a better understanding of the advantages and disadvantages. I feel confident too that the symposium will bring forcibly to the notice of medical administrators and politicians the need for mass chemotherapy as a tool that

brings tremendous advantages to those suffering from schistosomiasis and yet is associated with few risks to those who are treated. I am confident too that the symposium will highlight the sterling work done by Egyptian workers in this field.

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A SELECTIVE APPROACH TO THE SEARCH FOR SAFER SCHISTOSOMICIDAL DRUGS

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During the past five years the three most widely used drugs for the treatment of schistosomiasis throughout the world have been hycanthone and niridazole for infections caused by *Schistosoma mansoni* and *Schistosoma hematobium*, and the nitrofurant derivative, furapromidium (F-30066) for *Schistosomiasis japonica*. All three compounds are potent mutagens. Much evidence has been forthcoming indicating that many, if not all, mutagens are carcinogenic; in fact, more recently, both hycanthone and niridazole have indeed been found to be carcinogenic. Furapromidium, whose mutagenic activity is of the same order of magnitude as that of niridazole, has not yet been tested for its carcinogenic potential.

The nature and course of schistosomiasis are imposing certain restrictions on the design and use of drugs for the treatment of this infection. Since it affects such a large number of human subjects, even a low incidence of serious, delayed complications, such as mutagenic or carcinogenic effects, can involve a large absolute number of individuals. Furthermore, in a good number of cases, schistosomiasis is asymptomatic or causes no overt disease manifestations. In such cases, the benefits of chemotherapy for the individual are questionable unless serious, immediate, and delay-

ed side effects can be avoided. This applies in particular to young individuals infected with *Schistosoma hematobium*, in whom, at least in some parts of Africa, and in contrast to Egypt, clinical and pathological manifestations often disappear in adulthood. These factors should be taken into account when considering the use of any antischistosomal drug in the mass treatment of children whose life expectancies are longer and whose reproductive potential is greater than those of older individuals. It was stated by Rubidge et al. (1970) that «Urinary tract bilharziasis is a relatively mild disease in South Africa and that serious sequelae are rare. Hence, therapy must be safe».

If the mechanisms involved in the mutagenic and carcinogenic effects of a given drug differed from those producing antischistosomal activity, it should be possible to dissociate these and other undesirable toxic effects, from desired chemotherapeutic effects by suitable structural modifications.

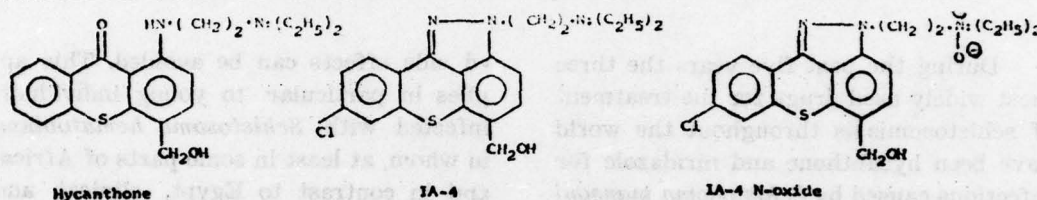
We have examined the feasibility of such an approach for the development of safer antischistosomal drugs.

Studies by Hirschberg et al. (1968) have shown that both lucanthone and hycanthone interact with DNA. This property could account for the mutagenic

and carcinogenic activities of hycanthone. The same investigators have shown that N-methyl lucanthone and N-methyl hycanthone fail to react with DNA; yet both compounds have antischistosomal activity. Therefore, a substituent in the proximate amino nitrogen (or a conversion of a secondary to a tertiary amine) abolishes reactivity with DNA, but does not eliminate antischistosomal activity.

Hence, different mechanisms indeed appear to be involved in the mutagenic and the antischistosomal effects of this class of compounds.

Another structural feature deserves consideration. Not infrequently, introduction of an electron withdrawing group, such as a chloro-substituent in the distal ring, is known to lower acute host toxicity.



These two structural characteristics are incorporated in a chloroindazole analog of hycanthone, IA-4, because the proximate nitrogen is a tertiary, instead of the secondary amine, and because this compound has a chloro-substituent in the distal ring.

Hycanthone and IA-4 are equiactive, at least in mice, although the indazole analog not only has lower mutagenic activity, but also a five-times lower acute intramuscular toxicity as determined by the LD₅₀.

Aside from its lower acute toxicity, IA-4, in contrast to hycanthone, is not teratogenic in mice. Hetrick & Kos (1973) have shown that hycanthone, in extremely low concentrations, induces malignant transformations of Rauscher virus-infected rat embryo cells, a property which this drug shares with many carcinogens. IA-4 even in 100-times higher concentrations did not exhibit this effect.

In mice infected with *Schistosoma mansoni*, a single intramuscular dose of hycanthone increases hepatic hyperplasia and produces, in a significant number of

animals, hepatocellular carcinomas (Haese et al., 1973).

IA-4, and for that matter also, oxamniquine, are devoid of a carcinogenic effect under these conditions (Haese & Bueding, in press).

Recently Sarma (in press) has found that 4 hours after administration of a single intramuscular dose of hycanthone to rats, there are double-stranded breaks in liver DNA. The same effect is seen with known hepatocarcinogens, while all of the non-carcinogenic analogs as well as IA-4, failed to exhibit this effect. Lucier et al. (1973) have reported that administration of hycanthone to rats is followed by a significant inhibition of the activity of hepatic microsomal drug metabolizing enzymes. Again, IA-4 lacked this hepatotoxic effect in equal or even higher doses. IA-4, when administered orally, is equally active as an antischistosomal agent as on intramuscular administration, while this is not the case for hycanthone. Furthermore, IA-4 has antischistosomal activity in rhesus monkeys infected with *Schistosoma mansoni*.

Many investigations have demonstrated the role of cell proliferation in enhancing the effects of carcinogens. Domingo et al. (1967) reported that in experimental schistosomiasis *mansoni* the effect of a hepatocarcinogen, 2-amino-5-azotoluene, is markedly potentiated, indicating that cellular proliferation occurred in the liver as a result of the deposition of eggs. Similarly, it was found that in mice infected with *Schistosoma mansoni*, hepatic hyperplasia, brought about by schistosome eggs deposited in the liver, is a predisposing factor for a hepatocarcinogenic effect of hycanthone (Haese et al., 1973). This was confirmed by a study which has just been completed in mice infected with *Schistosoma mansoni*. Again, hepatic hyperplasia in terms of foci or areas of basophilic cellular alterations were markedly increased following the administration of either a low (3 mg/kg or a high (60 mg/kg) intramuscular dose of hycanthone. In addition, there was a significant increase in neoplastic nodules in both groups and in hepatocellular carcinomas after administration of the high dose of hycanthone. The low dose (3 mg/kg) in mice was too small to have any chemotherapeutic effect because hatching miracidia were recovered from 84% of the livers in this group. Yet, this low dose was sufficient to induce an over five-fold increase in the areas of basophilic alterations and to produce a statistically significant incidence of neoplastic nodules. A 20-times higher dose (60 mg/kg) was required to produce a marked reduction in the number of worms and closely corresponded to the therapeutic effects of 3 mg/kg in man. Such a species difference in the therapeutic dose would be expected, because the surface rather than the weight of the animal is related to a pharmacologically active dose. Administration of either IA-4 or of oxamniquine under similar

conditions did not give rise to hepatocarcinomas and, with the exception of a single neoplastic nodule, the incidence of hepatic hyperplasia was not greater, but rather smaller, than in the control group of untreated infected animals (Haese & Bueding, in press).

In further studies of the effect of structural modifications on mutagenicity, N-oxides of thioxanthenones and of the indazole analogs were prepared. N-oxidation of the distal amino group consistently resulted in a marked reduction in mutagenicity. For example, N-oxidation of IA-4 yielded a compound whose mutagenic activity was 5 times lower than that of IA-4, while its antischistosomal potency in mice was similar to that of the latter compound, or that of hycanthone, when administered as a single intramuscular dose. The acute toxicity on intramuscular injection of IA-4 N-oxide was 3 times lower than that of IA-4 and more than 12 times lower than that of hycanthone. The mutagenic activity of this compound was only 2% that of hycanthone. Since these two compounds, on intramuscular injection are equipotent, the chemotherapeutic index of the two compounds is 117 and 8.3, respectively.

The N-oxide derivative of IA-4 as well as IA-4 itself is equally active on single oral administration as on intramuscular administration. This is of considerable interest because analysis of the muscular site into which hycanthone had been injected revealed the presence of a deposit which persisted at least 8 months in that tissue. The quantity of this material gradually decreased over this period, indicating either a slow destruction or a release into the general circulation. Analysis of this residue revealed five major and four minor components. None of them was identical with hycanthone. One has been identified as the

dimer of hycanthone, and the mutagenic activity of another one was 3 times as high as that of hycanthone itself (Fisher et al., unpublished observations). Slow release of one or several of these components might be related to, or might be synergistic with, the hepatocarcinogenic effect of hycanthone in mice infected with *Schistosoma mansoni*.

Hence, compared with a drug that has to be administered intramuscularly, an oral formulation not only is cheaper and simpler to administer, but also provides a significant additional safety factor.

IA-4 N-oxide also exhibits prophylactic activity, that is, when administered either intramuscularly or orally prior to, or one day after, cercarial infection, the worms do not develop to the adult stage, and apparently are destroyed. However, the doses required for this prophylactic effect are approximately 4-5 times higher than the curative doses. It remains to be determined whether this activity is sufficient for the development of a useful slow release preparation providing protection for at least several months. It also would be necessary to determine whether such a preparation is completely free of mutagenic activity.

Therefore, discrete structural modifications of the hycanthone molecule have

provided a compound whose mutagenic activity is less than 2% and whose acute toxicity less than 12 times that of hycanthone. Yet this compound had not only the same antischistosomal activity when injected intramuscularly, but in addition, and in contrast to hycanthone, is active when administered as a single oral dose, and, finally, has prophylactic activity.

An example of such a dissociation of therapeutic from long-term toxic effects is provided by another class of pharmacological compounds, the adrenergic beta blocking agents. Over ten years ago, the first β_1 -adrenergic blocking agent, pronethalol, was found to be carcinogenic (producing thymic tumors in mice). The manufacturer of this compound immediately withdrew the drug. Shortly thereafter it was found that mere introduction of an additional methoxy group in the side chain proximal to the naphthylene ring resulted in a compound devoid of carcinogenic activity but endowed with even greater β -adrenergic blocking activity. This drug, propranolol, is a widely used drug for the treatment of a variety of cardiovascular disturbances.

Therefore, this selective approach towards the design of safer and more effective drugs has proven its validity and feasibility with at least two different classes of drugs.

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EXPERIENCE IN BRAZIL WITH THE USE OF AVAILABLE SCHISTOSOMICIDES IN MASS TREATMENT CAMPAIGNS

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Mass treatment for schistosomiasis ideally refers to the universal treatment of whole populations living in endemic areas. However, as non-toxic drugs are not yet available for schistosomiasis, treatment should not apply to all members of such communities as with malaria. Vianna Martins (1952) defines it as being a simultaneous or almost simultaneous treatment of a large number of people representative of a population. Although the lack of single dose therapy in the past made it difficult to establish mass treatment for schistosomiasis, programmes have been carried out which could be considered as mass treatments, reaching large numbers of people infected by *Schistosoma* in a well defined population.

Programs of Mass Treatment in Brazil

Antimony compounds

Maciel (1929) first used antimony compounds in Brazil for mass treatment of schistosomiasis mansoni. He treated 1063 sailors (9% of the Brazilian Navy) in the period from 1923 to 1928. Tartar emetic was used in a total dose of 0.95 g intravenously, administered over a period of 10 days. He claimed 92% success in therapy.

In 1943 treatment of schistosomiasis became compulsory in the village of

Catende in the state of Pernambuco (Jansen, 1946). Seven thousand people were examined and 4,171 were found to have *S. mansoni* eggs in their stools. In the period from 1943 to 1947, 3,539 people started treatment, of which 3,334 completed it. The drug used was tartar emetic. Only one death was reported. Although this form of treatment was not widely accepted in the period from 1949 to 1952, 582 more people were treated. The efficacy of this therapy was assessed by stool examinations in the three months following therapy, and 64% of treated patients were found to have negative stools.

From 1951 onwards Sette (1953) set up a long term follow-up to assess treatment of schistosomiasis in Catende. He reviewed 1094 treated patients and compared them with a similar group of non-treated patients. He found that 40% of the treated group still passed eggs in stools as compared to 66% in the control group. Liver function tests were better in the treated group and only 1.7% of patients progressed to the hepatosplenic form as compared to 9% in the non-treated group. Since histopathological examinations had been carried out as a routine in those who died in the area before and after introduction of compulsory therapy for schistosomiasis, it was possible to analyse prevalence of schistosomal

lesions in the population. It was found that such lesions were prevalent in the order of 16.5% before treatment and 11.5% after treatment. As far as hepatic fibrosis is concerned, its prevalence was 5.4% before treatment and 1.3% after treatment. Although his data are very important, his control groups were too small (sometimes only 25 cases) to enable us to draw any definite conclusions. It is noteworthy that in the village of Catende, a hygiene education campaign was set up together with the compulsory treatment for schistosomiasis, and molluscicides were introduced, although these measures were not continued (Sette, 1953).

After the discovery of an endemic area in the town of Araxá, state of Minas Gerais, all those passing schistosome eggs in stools were treated using neo-antimonsan. A year later Silva (1955) showed that 85% of treated patients were still passing eggs in their stools. Such a high prevalence of positive stool examinations might be explained by either re-infection or by failure in therapy. The same high prevalence of positive stool examinations after treatment was found in the village of Redenção, in the state of Ceará. Silva (1960), commenting on this, states that re-infection may well explain the high prevalence of positive stool examinations in patients treated in Redenção, whereas in Araxá failure in therapy could well be the case. Neo-antimonsan however was successfully used in Fordlandia, in the state of Pará. Out of a population of 2,000, 130 patients were treated in the period from 1954 to 1956. In 1962 only 19 patients were found to pass schistosome eggs in their stools. These were treated (Freitas, 1972), and now Fordlandia is no longer an endemic area.

By 1956, 15,000 patients in the Northeast of Brazil had been treated by

the Ministry of Health through a national campaign (Silva, 1957a); 10,000 more were treated in 1957 (Silva, 1958). The drugs used were: 1) Neo-antimonsan in a total dose of 1 ml (8.5 mg Sb⁺⁺⁺) per kg b.w. intramuscularly over a period of 12 days; 2) Antimony dimercaptosuccinate in a dose of 40 mg/kg b.w. intramuscularly over six days; 3) Sodium antimonyl gluconate in a dose of 17 mg/kg b.w. intravenously over six days. About 80% of patients completed treatment and only one death was reported (Silva, 1957a). The cure rate was assessed by four stool examinations in the four months following treatment and was found to be 70% (Pinotti, 1957). This treatment was carried out by local clinics. One of them (Itaporanga) had 6,000 patients. Silva (1958) analysing the results of this campaign stressed that the elderly group of treated patients presented higher rates of negative stools. In Itaporanga the rate of positive stool examinations dropped from 78.5% to 59.5% (Silva, 1957b).

In the period from 1962 to 1971, 82,276 more patients were treated by the Ministry of Health. This figure does not include patients treated by health services in different states of the country (Freitas, 1972). The results of this campaign have not yet been analysed.

Freitas (1972) criticized governmental programmes for the control and treatment of schistosomiasis in Brazil — mass treatment included — chiefly because of lack of continuity.

Kloetzel (1963) treated 112 youngsters with an antimonial drug in the village of Gameleira, in the state of Pernambuco. Gameleira has 5,000 inhabitants and is located in an endemic area. A 90% decrease in stool egg excretion was found 1 year after treatment.

Following Davis' (1972) concept of mass chemotherapy specific to an age group, Prata and colleagues, from 1952 to 1973, treated 1,679 navy trainees in the state of Bahia. All those who joined the Navy during that time were investigated by stool examination and rectal biopsy, and those who were found to be positive were allocated to different schemes of treatment. More than 20 schedules were used and the cure rate was largely dependent on the kind of scheme used.

Hycanthone

The great advantage of hycanthone therapy has been the possibility of a single dose therapy, making it suitable for mass treatment (Figueredo & Prata, 1969).

Piza (1975), in the state of São Paulo, has the largest series of patients treated with hycanthone; so far 61,461 patients have been treated. The initial schedule recommended by the campaign against schistosomiasis in this state was 3 mg/kg b.w. but it was later reduced to 2.5 mg/kg b.w. This campaign is still in progress and its results have not yet been assessed. A complicating factor is that internal immigration is responsible for the ever increasing extension of the endemic area in the state of São Paulo. According to the Immigrant Selection and Guidance Service, at least 36,000 new schistosomiasis patients have moved to São Paulo in the period from 1973 to 1974.

In the period from 1973 to 1975, 25,798 patients were treated with hycanthone by the Ministry of Health. Of these 75% were from the states of Paraíba, Espírito Santo, Rio de Janeiro and Paraná. No data are available on the results of this treatment.

Bina & Prata (1970) treated 211 schistosomatic patients living in Varzea

Nova, an area where transmission of the disease was low. The age range was 2-74 years; 15 patients had the hepatosplenic form of the disease, while 196 had the hepato-intestinal form. Hycanthone was used in a single dose of 2.5 mg/kg b.w. intramuscularly. Only pregnant women and two other patients with contraindications were not treated. Side effects were nausea, vomiting, anorexia, dizziness, headache, drowsiness, sleepiness and pain at the site of the injection. However symptoms were only mild or moderate and not lasting more than 24 hr. In only four patients were positive stools found in five examinations after five months of treatment, and in only one after 16 months.

Hycanthone, in a single intramuscular dose of 3.3 mg/kg b.w., was used to treat 597 persons in the endemic village of Canabrava in the state of Bahia (Bina & Prata, 1974); 83% of the total population was treated, leaving only 7% of patients with schistosomiasis not treated. Treatment was given to the whole group over two days; the drug was well tolerated, with the frequency and intensity of toxic reactions and side effects similar to those observed in Varzea Nova. After five stool examinations 14 months later, 152 patients (25.5%) were still passing eggs in stools. Then 92 positive patients were re-treated with hycanthone, using the same schedule. There was one death probably caused by toxic hepatitis. The first stool examination after the second treatment was negative in 77% of the patients, in comparison with the 93.7% after the first one. This suggests the possibility of acquired resistance. The final stool examination 38 months after the initial treatment showed 19% of patients passing eggs. This percentage is considerably better than the pre-treatment value of 46.3%, and applies for all ages (Fig. 1).

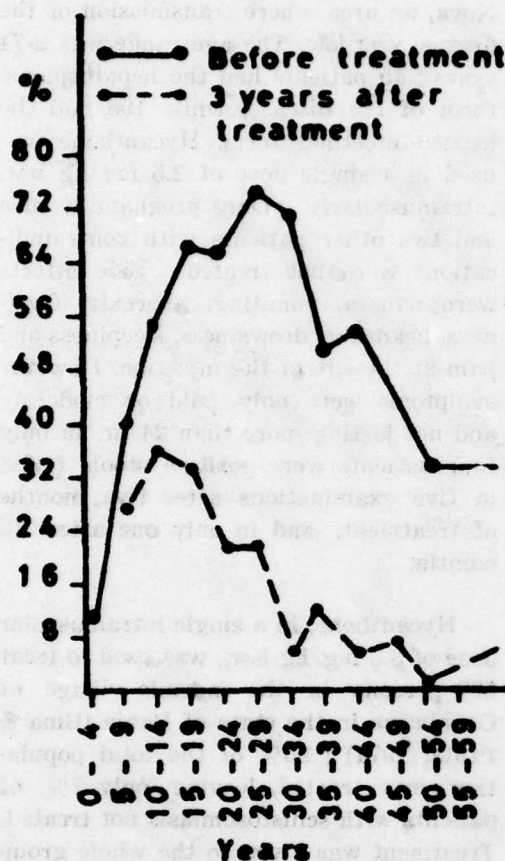


Fig. 1. Prevalence of Schistosomiasis measured by the presence of eggs in stools, before and after treatment, according to age groups.

Similar results were obtained by Aguirre et al. (1972) in the states of Rio de Janeiro and Rio Grande do Norte. Katz et al. (1970) treated 745 patients in the village of Baldim in the state of Minas Gerais. Only 16 pregnant women and another 22 patients with serious concurring disease were not treated. Hycan-thone was used in a single dose of 2.5 mg/kg b.w. intramuscularly. Side effects were nausea, vomiting, anorexia, muscle pain, headache, dizziness, and tenderness at the site of injection, but they were mild to moderate and disappeared in 24 hr. The percentage cure after 3 negative stool examinations was 95.6%. Katz stressed

the fact that he had already treated more than 9,000 patients without fatality or even jaundice.

Therefore in the past five years more than 100,000 people have been treated as part of controlled therapeutic programmes, and the manufacturers of hycan-thone claimed that by June 1975, 4,333,018 patients had been treated with that drug in Brazil.

Oxamniquine

Bina & Prata (in press) treated 75 children aged from 3 to 12 years in Taquarendi in the state of Bahia. This is an endemic area, where transmission has, however, been prevented.

An oral suspension of oxamniquine was used in a single dose of 15-25 mg/kg b.w.; 21% of the patients had one or more of the following side effects: dizziness, drowsiness, nausea and occasionally vomiting, but they disappeared spontaneously in 1-2 hr. The cure rate was 88%. Another group of 313 patients with the hepatosplenic form of schistosomiasis was treated by the same authors in Mirangaba (Bahia), where there is also no transmission of schistosomiasis. Oxamniquine was used in capsule form for adults in a dose of 12.5-15 mg/kg b.w., and in suspension form for children in a dose of 20 mg/kg b.w. One or more of the following symptoms were seen in 56% of patients: dizziness, drowsiness, headache, nausea (7.34%), vomiting (2.85%). These side effects disappeared in the two hours following treatment. The cure rate was assessed by five stool examinations in the six months following treatment, and 84% of patients were found to have negative stool examinations.

The same authors treated 286 patients in the endemic area of Boa Esperança in the state of Bahia. The number

of patients treated represented 87.7% of the whole population and 11.4% of them had a severe form of the disease. The oxamniquine dose was the same and side effects were similar to those previously reported for Mirangaba.

Coura et al. (1975) treated 504 patients in two different villages in the Rio Doce basin in the state of Minas Gerais. They were 310 patients in São Geraldo, comprising the whole population, and 194 patients in Itanhomi (25% of the population). Oxamniquine was used in a single dose of 12.5-18 mg/kg b.w. Side effects were dizziness (13.6%), nausea (2.3%), headache (2.3%), vomiting (1.6%), abdominal pain (0.9%). Two patients had psychiatric disturbances: one became aggressive and the other exhibited perceptual disturbances. Apart from these two patients, side effects were mild and transient, not requiring medication. Evaluation is still in progress, but so far 57.2% of patients show negative stools.

Katz & Zicker (personal communication), using a single oral dose of oxamniquine of 20 mg/kg b.w. for children and 15 mg/kg b.w. for adults, treated 220 patients in the village of Peri Peri in the state of Minas Gerais. Side effects were mild and the authors recommend the drug for the treatment of communities. The cure rates four months after therapy, assessed by 2-4 stool examinations, were found to be 65.5% for children and 82.4% for adults.

The manufacturers stated that by June 1975 oxamniquine had been given to more than 100,000 patients without fatality or even jaundice.

In conclusion, apart from the two cases of neuropsychiatric disturbances reported by Coura et al. (1975, personal communi-

cation), no serious complication has been observed with oxamniquine.

Comments

In the past mass treatment of schistosomiasis was done cautiously with antimony compounds and large numbers of patients were treated by the Ministry of Health through health clinics. Toxicity of antimony compounds, long term therapy, difficulty in injecting the drug and the possibility of re-infection hindered the pilot projects. Furthermore patients cooperated poorly and the mass treatment in the village of Catende left doubts as to the applicability of this kind of treatment in Brazil.

This situation was not altered by the use of Niridazole once it was found that large numbers of patients—particularly those with hepatosplenomegaly complained of various neurological symptoms.

During the last six years however, the introduction of single dose therapy has made mass treatment of schistosomiasis easier. Hycanthone has been used in various pilot projects and at present two very large campaigns are still in progress. Unfortunately, with the treatment of more cases, reports of severe toxic hepatitis have appeared (Andrade, 1974) and the possibility of resistance after the first dose, together with accusations of teratogenic, carcinogenic and mutagenic effects — although not substantiated (WHO, 1974), have reduced the use of hycanthone as a drug for mass treatment. However it has been used in this way in Brazil with more than 100,000 patients.

Oxamniquine in oral form raised optimism as a suitable drug for mass treatment of schistosomiasis, but so far it has only been used in pilot projects.

Perhaps we are not far-away from introducing mass treatment for schistosomiasis as we do for malaria. This is not possible with hycanthone and as yet we do not know whether it will be possible with oxamniquine. We may have to await the emergence of a new drug.

It is evident that mass treatment of schistosomiasis is the best form of treatment in a non-endemic area, as was seen in Fordlandia where the disease was

eradicated by specific treatment, and in Varzea Nova where it was controlled.

The Brazilian experience shows that during the long term, treatment may decrease the prevalence of the disease, even in endemic areas, although it is difficult to assess it in terms of the general control of the disease.

It appears that treatment of schistosomiasis prevents the appearance of serious forms of the disease.

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MASS CHEMOTHERAPY CAMPAIGNS FOR THE CONTROL OF SCHISTOSOMIASIS IN EGYPT

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Human schistosomiasis is still the scourge of the great majority of rural inhabitants of Egypt, although Egypt was one of the first countries to apply mass therapy campaigns, soon after the discovery of an effective schistosomicidal chemotherapy.

Since drug therapy can cause cessation of egg laying, it can remove the factor most pathogenic to host tissues. When given during the active stages of the disease, it can also reverse many pathological changes. Elimination of the excretion of ova will block the most essential stage in the maintenance of transmission.

However, we do not yet have an ideal absolutely safe therapeutic drug, efficient against all stages of the disease, that could be applied economically on a large scale and be acceptable to the population.

No systemic prophylactic drug has yet emerged, and any drug showing such a property in experimental animals would still require elaborate assessment before it could be applied to man.

In spite of the great number of people suffering from bilharziasis and the great efforts expended in searching for effective schistosomicides, only few drugs have

reached the clinical stage as drugs of proved value for mass therapy campaigns.

Past Experience with Mass Therapy in Egypt

Soon after the discovery of the efficiency of the trivalent organic antimonials, mobile health units were established in Egypt in 1920 for diagnosis and chemotherapy, with special stress on treating school children and active field labourers. Treatment helped much in decreasing the morbidity and the serious complications of the disease, although it did not significantly lower incidence or prevalence. Probably the great success apparent in these campaigns applied to Upper Egypt, where the infection rate was low, transmission seasonal rather than perennial, and where there existed only one species of the parasite and its snail host.

Those campaigns were designed so as to take place immediately before the seasons of maximum transmission, especially when snail control was also applied at the same time.

Improvements in the methods of diagnosis adopted at field level gradually diminished the negative cases missed, especially those with intestinal schistosomiasis.

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miasis. The perfecting of the calling and follow-up systems, through the help of local social health workers, added much to the success of such campaigns, especially when health education was also applied.

However, it was not always possible to reach the whole rural population so as to obtain specimens of their excreta. Moreover, many cases of immature or unisexual infections were always missed. Among the positive cases discovered, there always was a certain number of individuals unfit for treatment and others whom side effects prevented from completing their prescribed courses.

Legislation requiring freedom from infection on admission to school, upon employment, or on army recruitment has proved of value, provided that facilities for diagnosis and treatment were available in the institutions concerned.

The establishment of rural health units, which now amount to 2000 units, are sited no more than a distance of 3 km from rural inhabitants, and which have the capacity of treating 3 million patients yearly, has added much to the facility of follow-up for some time after the patients have finished their courses.

The new methodology that has been adopted, i.e. a shift from the classical courses of therapy to the widely spaced dosage in field practice, has greatly minimized the side reactions which in many cases stopped people from finishing their treatment.

Yet, in spite of the introduction of different compounds for oral or parenteral use, trivalent organic antimonials have been the common drugs used in the mass treatment of both the urinary and intestinal forms of the disease. The occasional occurrence of sudden shock among

patients treated by Stibophen limited its use for some time, until it was found to be related to poor storage of the drug in powder form during World War II. But the condition did not arise with the well-bottled forms. Such accidents had sometimes ended fatally, due to associated intravascular hemolysis culminating in glomerulo-tubular block with renal failure.

Different schemes of intensive therapy with antimonials were applied, but, because the majority of the treated cases could not tolerate such intensive therapy, and some of them ended fatally, this mode of therapy was discarded in field practice.

Miracid D was applied as an oral schistosomicide, especially for school children. Due to the frequency of side reactions, however, its use remained limited. Moreover, the cure rate in *Schistosoma mansoni* was found to be low.

Immunological processes seemed to play an important role in the defense mechanism which could be stimulated by drug therapy; this minimizes the need for frequent repetition of therapy or prolonged courses. In quantitative egg output studies, it has been found that, when patients, especially children and young adults, were re-exposed to infection after preliminary therapy, re-infection resulted in low density egg output and showed better response to chemotherapy.

In our pharmaceutical laboratories, progressive interest was directed towards the elaboration and modification of available effective drugs so as to lower their toxicity and assure their stability without lowering their efficiency. Local industrialization of such drugs assured their availability at low cost whenever desired.

Mass treatment of the whole rural population was found to be unsafe when applied in certain endemic areas on a large

scale, including non-infected cases, by suppressive courses of various antimony preparations.

Blood drug estimations that were carried during different courses of therapy proved that drug levels did not approach those found to be lethal to the worms *in vitro*. The therapeutic effect was found to be due mainly to immunological tissue reactions. It was also found that brief exposure to high concentrations of some of these drugs, when followed by exposure to much lower dosage, could give better results than either type of exposure.

Reduction of Niridazole dosages, combined with certain steroids with immunosuppressive characters, as well as administration of small doses of saline diuretics during the advised courses of therapy, gave promising results in cases of gross morbidity, in whom treatment was previously considered to be contra-indicated.

The application of a second injection of Hycanthone 1-3 months after the first dose raised the cure rate, in haematobiasis, in school children, to about 90% when it was used in a mass campaign in 2 villages near Cairo. In adults, diminution of Hycanthone dosage did not give beneficial results equal to those observed in cases of mansoniiasis in the northern parts of the Nile Delta.

The frequent appearance of certain immunoglobulins, coupled with a huge enlargement of the liver and spleen and with sustained low grade pyrexia, responded to a combination of specific schistosomicides with certain antibiotics. This condition proved the frequent occurrence of associated intercurrent bacterial infection. Niridazole and Hycanthone gave better results in such cases than did antimonials, and obviated the need of resort-

ing to surgical management of many of these cases.

Several international and foreign scientific agencies were associated in such campaigns in that they offered many of the needed materials and equipment, as well as the necessary expert advice during operation or during post-therapy evaluation.

From the above experience in our country, it has been concluded that periodic mass chemotherapy campaigns especially when applied to susceptible sectors of the population, early in the evolution of the disease, can be considered the most effective, cheap and rapid measure for control of the disease especially in areas under perennial irrigation.

Present and Future Prospects of the Mass Treatment Campaigns in Egypt

In the final evaluation of the programme of the WHO/Egyptian Government Bilharziasis Control Project (Egypt 49) operating in Beheira Province near Alexandria, in 1968-69, which aimed at controlling the disease by proper snail control, it was astonishing to find that there was no fall in either the transmission or the prevalence rates of the disease in the areas under control, as compared to the non-treated areas. Even the conversion rate among negative children below 6 years of age at the start was found to be higher in the operational area of the project. Attention was directed to the importance of utilizing egg counting techniques as an index of the severity of infection. Black eggs were no more considered as signs of relapse, as they only indicated the continued presence of necrotized immature ova which lacked the stimulus needed for easy extrusion in human excreta. This project proved that although there was a consistent reduc-

tion in snail densities in water courses of the area under study, cumulative infection rate among the inhabitants continued, which denotes that mollusciciding in non-isolated irrigated areas as a single measure of control was unsatisfactory. Since 1970, human treatment was applied in addition to snail control, and the project has since become a demonstration and training area for applying all means of schistosomiasis control used collectively or separately.

In 1968-71, the Fayoum Project was established in Middle Egypt. In this project, whenever possible human treatment was given simultaneously with snail control by certain molluscicides and herbicides. Niridazole was utilized for school children and tartar emetic for adults, treatment to be repeated yearly in cases positive for bilharziasis. The surveys consisted in one sample examination, as this area is only infected with *S. haematobium*. In the final evaluation of the Fayoum project in 1972, the snail density and the infection rate among the population had been greatly reduced. Children from 0-2 years old did not show a single case of infection, while those from 2-5 years old proved positive at a rate of only 2.61%. Up to now prevalence rates among other age groups did not exceed 10-18%, as compared to 50-60% at the start of the project, and the cure rate by the drugs used attained an apparent parasitological cure of 85%.

The success achieved by this project encouraged our government to formulate a wide national control programme to be applied during the next 10 years, starting in Middle Egypt and to be followed by Upper Egypt and finally by Lower Egypt. Enforcement of the existing means of control will be placed in the hands of a specified organization to integrate and execute all the accepted means of control,

according to priorities related to the ecological conditions of each governorate.

Indirect means of diagnosis by utilizing the sero-immunological techniques will be given greater emphasis as screening aids alongside of direct parasitological methods, be it during the pre-treatment surveys or the post-therapy evaluations. The establishment of the «Bilharz Research Institute», with its well-organized field units, will be helpful in encouraging the applied field researches needed, and in encouraging the organization of teams of workers from different scientific and social specializations. Co-operation of the Institute with local health authorities will have a favorable impact on the services available and stimulate the co-operation of the people. Moreover, the Institute will be an ideal place for field training for all cadres needed.

Most of our Medical Faculties have now started to establish special departments for the study of tropical medicine and endemic diseases, so as to be actively associated in developing research in these vital fields. Several additional technical institutes, such as nurse training schools and institutions for recruiting social health workers, especially trained in rural field practice, are under construction. In addition, health visitors are to attend all elementary schools.

Statistical facilities, utilizing a computer system, will be used for cost-benefit estimation, so as to indicate the economic aspects of such intended long-term projects.

Luckily, most of the available drugs are not, or have not yet been shown to be, either mutagenic or carcinogenic and many of them can be given safely in early pregnancy, if need be in special schedules, when the clinical manifestations are annoying. There was also no definite

evidence of any drug resistance when these drugs were repeatedly administered, unless there existed an inherent metabolic or genetic refractoriness in certain strains of the parasite.

Greater attention has been given to the application of existing medical knowledge. Several authors are preparing special review volumes to be published by the Egyptian Academy of Science and Technology, and are expected to be available soon. Also, since 1974, a special journal has been issued to discuss new facts in a form adapted for local communities, with the aim of keeping a balance between human infection and its environment. Such efforts will definitely encourage the formation of health teams oriented to the local needs of our rural community, who will have enough experience in all scientific and social aspects of such disease problems, especially those dealing with the more vulnerable sectors of the population.

Summary and Discussion

We have seen that attempts at controlling human schistosomiasis through mass chemotherapy campaigns in Egypt during the past 50 years, despite limited successes, did not lower its prevalence. This was largely due to the increase in land reclamation without implementation of the necessary control measures. The limitations of the previous means of control showed that the drop in the prevalence rate did not exceed $\frac{1}{2}$ -1% yearly, which indicated that proper control measures at the present standard would need to be continued for 30-40 years. This would cause a loss of not less than 15,000 million Egyptian Pounds in our national income. Thus, it will be necessary to enforce active measures as soon as possible. The investment will be necessary for the develop-

ment of our rural communities in the near future.

In the mid-1960ies the schistosomal life cycle in East Africa was mathematically simulated as a computer model by MacDonald (1965). He found that the results of reducing exposure to infection, of reducing snail density and of proper rural sanitation were so slow and elaborate as to be disappointing when applied on a large scale. He recommended the priority of regular periodic campaigns of diagnosis, and treatment for every infected individual to be conducted at least once yearly, utilizing well-designed effective schedules of chemotherapy, that would fit every positively infected case. This control measure alone produced a fall in worm load to a level which was almost identical with that obtained by other control measures combined when applied for long periods. He also stressed that mass chemotherapy campaigns alone, when perfectly applied and properly sponsored, could obtain the same objectives as other methods combined in a period not exceeding 3-5 years, to be reinforced later by all possible measures available.

A similar conclusion was also later realized by Paulini in Brazil and by other workers. Application of treatment alone would save a lot of money and effort that are expended when all control measures are applied collectively at the same time. Such a programme, in areas under perennial irrigation and of high endemicity, is expected to pass the breaking point of the worm load necessary for maintaining transmission, and if applied for a prolonged period to lead even to the eradication of the disease.

Several authors have tried different schedules of modern drugs, given orally or parenterally, for mass-chemotherapy, either suppressive or curative, with promising results.

In conclusion, to ensure the success of such mass control measures on a country-wide national level, we have to stress the following basic principles :

1. Basic rural health service, however humble at the start, must be available, with reinforcement of the elements which are considered to be technically, economically and administratively feasible.

2. Study of the main technical, economic and administrative barriers in field practice for every locality, so as to solve them through local scientific and social efforts as soon as possible.

3. A persuasive rationale for the government or other donor agencies, so as to sustain their support for such control measures for prolonged periods.

4. A study of the effect of the disease on employment and on agricultural or rural development with its rapid growth of population and its economic achievements.

5. Development of public education ; educational institutions must cooperate during the administration of such campaigns, with increasing emphasis on reducing water and soil pollution by human excreta.

6. Better salaries and more incentives for health workers. These are necessary in a field which can contribute much to solve many of the emerging difficulties.

7. Facilities for epidemiological and ecological health studies. It is also necessary to periodically re-evaluate and reassess the situation so as to readjust control policies to any change in local challenging factors, apart from the periodic mass therapy campaigns.

8. Inclusion of priority for all rural health measures in irrigation and water resource development programmes, including quarantine of new immigrants for purpose of mass chemotherapy. Such programmes must also consider the quality of human life rather than be strictly oriented to economic development.

Since in rural communities basic health services are still lacking, there is little support of the widely held notion that the longevity and growth of the population has occurred as a result of mass control programmes of parasitic and communicable diseases. Improvement actually has been influenced by factors of general development, which have increased man's resistance to disease without eradicating their causal factors. It is a paradox that most of the parasitic and communicable diseases in developing countries have not yet been properly tackled, except for a few diseases, and that the outlook is for increase in the absolute number of cases on account of national population growth with continuously higher rates of infection.

I consider it essential that symposia be periodically held to review past, present and planned future efforts, which should be thoroughly discussed in the light of available national and international knowledge. All measures before their indiscriminate generalization or wide application should be carefully scrutinized and evaluated.

Further research efforts, both academic and applied, need to be encouraged in this field, for better tools adapted to our local needs to be available.

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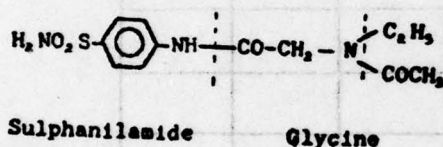
SUBCOMMITTEE SESSIONS

SULPHONAMIDES WITH SCHISTOSOMAL ACTIVITY

H. Horstmann, R. Gönnert, P. Andrews and J. Pellegrino

*Bayer A.G., Wuppertal, German Federal Republic and
Institute of Biological Sciences, Belo Horizonte, Brazil*

A few years ago a compound, prepared in our sulphonamide research programme and screened parasitologically, was found to have a weak but definite activity against *Schistosoma mansoni*, at high doses.



As you can see, this compound is a derivative of sulphanilamide by substitution with a glycyl residue. The glycyl-nitrogen atom is also alkylated and acylated in a specific manner.

Sulphanilamide and its derivatives possess an antimicrobial activity, particularly against bacteria and protozoa. However, sulphonamides with a schistosomicidal activity are unknown to date.

We have therefore followed this clue, interesting also theoretically, and have tried to find a useful drug by chemical modifications of the primary compound.

We would now like to report on the results of this work. At first we widely varied the nature of the acyl residue. A

selection of the compounds obtained is shown in Table 1.

Remarkable in this table is the high specificity of the acyl residue: only the acetyl derivative (No. 3) and the sterically very similar trifluoroacetyl derivative (No. 8) are active. All other derivatives are completely inactive even in high doses.

The importance of the acyl residue is further emphasised by the fact that the non-acylated compound (No. 1) is also inactive.

Table 2 demonstrates the influence of the alkyl residue for a constant acyl residue, the acetyl group.

One can clearly see that the activity starts at the ethyl derivative, runs through a maximum at 3 C-atoms (No. 19) and is yet just observable with 5 C-atoms in the chain. The dependence of activity on the degree of branching in the alkyl chain is evident: for the same number of C-atoms the branched compound is always more active than the straight chain analogue. Only the tert. butyl compound (No. 23) is an exception.

Similar correlations between structure and activity were also found in the corresponding trifluoroacetyl series.

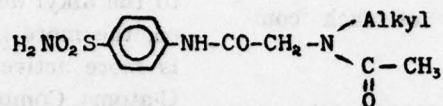
Table 1. $\text{H}_2\text{NO}_2\text{S}-\text{C}_6\text{H}_4-\text{NH}-\text{CO}-\text{CH}_2-\text{N} \begin{matrix} \text{Acyl} \\ \text{C}_2\text{H}_5 \end{matrix}$

No	Acyl	Single dose (mg/kg mouse) applied on 5 successive days				
		2500	1000	500	250	100
1	-H	0				
2	$\text{O}=\text{C}-\text{H}$	0				
3	$\text{O}=\text{C}-\text{CH}_3$	2	2	0		
4	$\text{O}=\text{C}-\text{C}_2\text{H}_5$	0				
5	$\text{O}=\text{C}-\text{CH}_2\text{Cl}$	+	0			
6	$\text{O}=\text{C}-\text{CH}_2\text{OCH}_3$	0				
7	$\text{O}=\text{C}-\text{CHCl}_2$	+	0			
8	$\text{O}=\text{C}-\text{CF}_3$	3	2	2	2	0
9	$\text{O}=\text{C}-\text{CCl}_3$	+	0			
10	$\text{O}=\text{C}-\text{C}_6\text{H}_5$	0				
11	$\text{O}=\text{C}-\text{OC}_2\text{H}_5$	+	0			
12	$\text{O}=\text{C}-\text{NHCH}_3$	+	0			
13	$-\text{O}_2\text{SCH}_3$	+	0			
14	$-\text{O}_2\text{S}-\text{N} \begin{matrix} \text{CH}_3 \\ \text{CH}_3 \end{matrix}$	+	0			

+ toxic; 3 cure; 2 effect; 1 slight effect;

0 no effect.

Table 2.



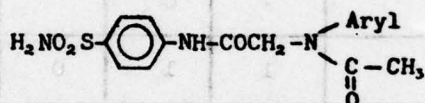
No	Alkyl	Single dose (mg/kg mouse) applied on 5 successive days				
		1000	500	250	100	50
15	-H	0				
16	-CH ₃	0				
17	-C ₂ H ₅	2	0			
18	-C ₃ H ₇ n	1	1	0		
19	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ -\text{CH} \\ \diagdown \\ \text{CH}_3 \end{array}$	3	3	3	1	0
20	-C ₄ H ₉ n	2	1	0		
21	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ -\text{CH}_2-\text{CH} \\ \diagdown \\ \text{CH}_3 \end{array}$	3	2	1		
22	$\begin{array}{c} \text{H} \\ \diagup \\ -\text{C}-\text{CH}_2\text{CH}_3 \\ \diagdown \\ \text{CH}_3 \end{array}$	3	2	1	0	
23	-C(CH ₃) ₃	1	0			
24	-C ₅ H ₁₁ n	2	0			
25	$\begin{array}{c} \text{H} \\ \diagup \\ -\text{C}-\text{CH}_2-\text{CH}_2\text{CH}_3 \\ \diagdown \\ \text{CH}_3 \end{array}$	3	2	0		
26	-CH ₂ -CH=CH ₂	0				
27	-CH ₂ -C≡CH	0				
28	-CH ₂ -C ₆ H ₅	0				

We obtained very interesting results when we turned our attention from the alkyl substituted derivatives to the aryl substituted derivatives. Table 3 shows a representative selection of such compounds.

The high activity of the 4-tolyl compound (No. 34) encouraged us to prepare further compounds with alkyl residues in the *para*-position to the aromatic amino group. The results obtained are shown in Table 4.

It is seen that the activity improves with the increasing number of C-atoms in the substituent, runs through a maximum at 4 C-atoms and then falls off. Similar to the alkyl derivatives already mentioned, the more highly branched compound is more active for the same number of C-atoms. Compound No. 45, which will be referred to as BAY d 9778, represents the activity optimum and was therefore selected for more thorough examination. It is approximately a hundred times more active than the ethyl compound mentioned at the beginning of the talk.

Table 3.













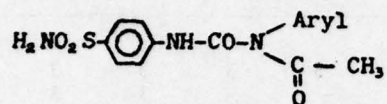
No	Aryl	Single dose (mg/kg mouse) applied on 5 successive days				
		1000	500	250	100	50
29		+	2	0		
30		1	0			
31		+	+	+	0	
32		+	0			
33		0				
34		2	2	2	1	0
35		2	1	0		
36		0				
37		0				
38		0				

Table 4.



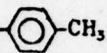
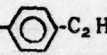
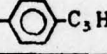
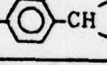
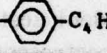
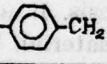
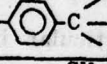
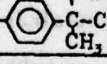
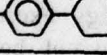
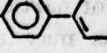

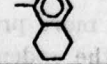
No	Aryl	Single dose (mg/kg mouse) applied on 5 successive days							
		1000	500	250	100	50	25	10	5
39		2	2	2	1	0			
40		+	3	3/2	2	2/1	1	0	
41		3	3	3	2	2	2	0	
42		+	3	3	3/2	3/2	2/1	1	0
43		3	3	2	2	2/1	1	0	
44		+	+	+	3	3/2	3/2	1	0
45		3	3	3	3	2	2	1	0
46		+	3/2	3/2	0				
47		+	3	3	3/2	3/2	2	0	
48		3	3/2	3/2	2	0			
49		3	3/2	3/2	1	0			
50		0							

TABLE 5. Oral and subcutaneous application of BAY d 9778.

Animal		Dose (mg/kg) five times on five consecutive days							
		1000	500	250	100	50	25	10	5
Mouse	p.o.	3	3	3	3	2	2	1	0
	sc.	+	+	3	3	3	2	1	0
<i>Saccostomus campestris</i>	p.o.		2	2	2	2	2	1	
	sc.				2	2			
<i>Mastomys natalensis</i>	po.		3	3	2	2	1	1	0
	sc.				3	3	2	1	1
Syrian hamster	po.	3	3	3	3	2	2	1	0
	sc.	+	+	3	3	3	3	2	0
Cebus monkey (3x)	po.				0	0			
	sc.				0	0			

+ Toxic

3 Cure

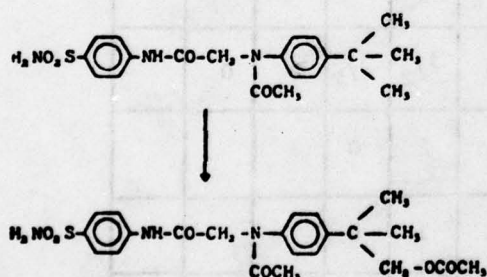
2 Effect

1 Slight effect

0 No effect

Table 5 shows the results obtained with BAY d 9778 in various rodent species. One of us (Pellegrino) studied several of the most interesting substances on Cebus monkeys. All compounds studied, including BAY d 9778, were found to be inactive.

BAY d 9778 and its Metabolite



Since the substance is also inactive *in vitro*, there existed the possibility of the active principle of this compound being a metabolite produced by the rodent. BAY d 9778 was therefore applied subcutaneously to mice in high doses. A me-

tabolite was isolated from the feces which was active in rodent tests. Its structure was elucidated spectroscopically and confirmed by synthesis. It was a derivative of the starting material, hydroxylated in the tert. butyl group and then acetylated.

It is of particular importance that the N-acetyl group, essential for its activity, «survives» metabolisation.

Although the metabolite has a slight effect on the egg excretion in Cebus monkeys, we do not believe that the hydroxylation is of particular importance for activity. This may already be concluded from the fact that metabolisation occurs in a part of the molecule which is not essential for activity.

We think it more probable that the monkey, unlike the rodent, de-acetylates BAY d 9778 and thereby inactivates it.

Due to the lack of activity in monkeys, testing on humans is not foreseen at the present time.

BENEFIT VERSUS RISK IN ANTI-SCHISTOSOMAL DRUGS IN EGYPT

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In other severely debilitating and probably rapidly fatal diseases, treatment with even risky drugs may be permissible. But with regard to bilharziasis, in most cases the patient is an ambulant active member of the community, who is usually encouraged to take treatment against his ailment. Moreover, treatment of bilharziasis is mostly conducted as a community or mass treatment, individual therapy being restricted to a low percentage of cases.

In Egypt, antibilharzial therapy is largely a governmental function carried out free-of-charge in the various rural health units and endemic diseases hospitals, which are widely distributed all over the country, especially in rural areas. Since the Government is the responsible body, it is the function and the responsibility of the Ministry of Health to provide for these patients the most effective, safe and well-tolerated antibilharzial compounds, which, from the financial point of view, are relatively cheap.

Thus, if we allow a certain degree of risk in the treatment of the individual case, who is under the direct supervision of the private treating physician or practitioner, such a degree of risk is not permissible in the case of community or mass treatment measures, especially if we take into account that in most cases the bilharzial patient is ambulant.

Because in Egypt antibilharzial therapy is essentially a governmental function and responsibility, no antibilharzial compound is recommended for mass therapy unless it has been subjected to a long series of sequential, acid, tests. Such a compound must at first prove to be effective, safe to use, and reasonably well tolerated when tested on in-patients in the Institute of Research for Tropical Medicine, as well as in other reliable centres in universities and research establishments, for a reasonable period of time. Then an out-patient probing is carried out to attest all parameters on ambulant cases. Thereafter, the compound is subjected to a semi-mass or community field trial, in order to assess its final efficacy and acceptability before recommending it for mass treatment schemes.

For quite a long time, trivalent antimonial compounds were applied for mass antibilharzial therapy in Egypt, by either the intravenous or the intramuscular routes. Since 1920 long experience has been gained from their mass application. Recently radio-isotope and activation analysis studies resulted in recommending their use twice weekly or once weekly in order to increase their safety range without materially affecting the efficacy level. This regimen caused a remarkable lowering of the toxic reactions of antimony, especially on the cardiac muscle. However, for the intramuscular compound

Stibophen, there occasionally occurred another, auto-immune process, which imperceptibly led to acute intravascular haemolysis and acute renal failure: an emergency that needs resuscitative measures with, in particular, intravenous corticosteroids to save the life of the patient. However, the prolonged and continuous use of trivalent antimony compounds has made them at least from the point of view of the patient, the favourite drugs for antibilharzial therapy, to the extent that many patients who have been treated with other, simpler, modes of therapy deny that they had previously been treated for bilharziasis and unnecessarily seek parenteral therapy with antimonial compounds. It is worthy of note that antimony compounds, as represented by potassium antimony tartrate, proved to be devoid of any mutagenic or carcinogenic effects.

Lucanthone was used in Egypt in the daily oral dose of 10 mg/kg b.w. for 20 consecutive days, but it proved, in the long run, to be non-acceptable for mass treatment schemes, not only due to its low cure rates in both *Schistosoma haematobium* and *S. mansoni* infections, but also due to the high degree of absenteeism and the relatively high percentage of side effects, mostly gastro-intestinal.

Many other drugs of the alkane series and of other series of chemicals could not stand the test of time in Egypt, even with regard to individual therapy, and were therefore abandoned.

Metrifonate, after extensive studies and alterations of the dose regimes, proved to be an effective and relatively safe mode of therapy for the oral treatment of *S. haematobium* infection in man. Being a choline-esterase inhibitor, any possible side-reactions can simply be treated with belladonna alkaloids or with

atropine, and no fatalities whatever were recorded even in critical or high risk cases.

According to the present parameters, it was found to be devoid of any potential carcinogenic, mutagenic or teratogenic effects, at least in the therapeutic doses applied for the time being, which proved to be effective, giving more than 90% cure rates. Even choline-esterate inhibition was considered a peripheral change that did not affect, or was not related to, central systemic reactions.

Niridazole is also a very effective schistosomicidal compound for the treatment of both *S. haematobium* and *S. mansoni* infections. The commonly met with gastro-intestinal side effects were remarkably reduced, by giving it for only 3 days, without notably affecting its efficacy. It was proved by mass field experiments that it did not materially affect the cardiac muscle, even in active ambulant children. Rare neuropsychiatric reactions may occur as a result of treatment of complicated intestinal cases. This is due to the increased blood level of the unmetabolized product, which results in the stimulation of the subcortical centres. The phenomenon can be immediately controlled by a single parenteral dose of chlorpromazine. The condition is not fatal though apparently alarming. Concomitant oral chlorpromazine administration with niridazole, however, did not relieve, but even potentiated the neuropsychiatric side effects, probably simply through raising the optimal threshold. The claim of its potential carcinogenic effects is based on work in which far greater doses were applied than those used in man. Such data are difficult to extrapolate to man.

Hycanthone was tried in Egypt for the treatment of both *S. haematobium* and *S. mansoni* infections. It proved to

be of moderate therapeutic efficacy, but had the advantage of easy application as it was given in the form of a single intramuscular injection containing about 3.0 mg/kg b.w. of the drug. The drug was tried at the Institute in the oral base form, in the parenteral sulfamate form and the parenteral methane-sulphonate form, which is now the only one accepted for therapeutic use in man, since our long experience with it indicated that the last form of the compound was relatively more effective. A pilot field trial was scheduled, but was postponed due to the world-wide outcry concerning the drug's possible mutagenic, teratogenic and carcinogenic effects. Controversial opinions were given by eminent research workers regarding these points and the position awaits firm evidence that would either allow or prohibit the use of this compound for individual or for mass use in anti-bilharzial therapy. It is, however, to be noted that hycanthone has been widely used in Iraq, in Brazil, and in other countries, and that the total number of patients so far treated with Hycanthone amounts to more than one million. As it is claimed to be a potentially hepatotoxic drug, it was recommended only for the treatment of uncomplicated bilharzial cases up to now, and was not officially recommended for mass antibilharzial treatment in Egypt. It was even suggested that it can be suspended for individual therapy until further evidence of its safety was provided. We are awaiting the results of research on this very subject being carried out in the U.S.A.

A newly introduced tetrahydroquinoline compound, called oxamniquine, when administered parenterally proved to be of no value in the treatment of both *S. haematobium* and *S. mansoni* infections in man. But given orally this compound proved to be effective in the treatment of *S. mansoni* infection, at a dose of 20 mg/kg b.w. daily for 3 consecutive days, a relatively higher dose than that used in Brazilian experiments. Moreover, it proved to be effective in the treatment of complicated cases of intestinal schistosomiasis mansoni in which other antibilharzial compounds were ineffective or were found to be contraindicated or hazardous to use. Its effect on creatinine phosphokinase has not as yet been assessed, though the compound proved to have no conspicuous deleterious effects on the hepatic and the renal functions or on the haematological picture, even in complicated *S. mansoni* cases.

When the effect of oxamniquine on creatinine phosphokinase has been investigated, a pilot field trial will be conducted in order to finally assess its practical use in the mass treatment of *S. mansoni* infection, in view of the fact that up till now it has proved to be devoid of any teratogenic, mutagenic or carcinogenic effects, at least in the applied therapeutic doses.

The problem may ultimately lie in the cost of treatment, as it appears to be prohibitively higher than can be afforded for mass treatment schemes.

VALUE OF ETRENOL IN THE PERIODIC TREATMENT OF BILHARZIASIS IN IRAQ

Hikmat Baquir

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Etrenol has previously been tried in Iraq in the treatment of Bilharziasis. The objective of this paper is to demonstrate the value of Etrenol in the periodic treatment of those still positive for Bilharziasis after a first treatment at intervals of three months with special emphasis on the timing of the start of treatment as related to the transmission season. Emphasis is placed on this objective, since other relevant observations related to side effects and the relation of the treatment to age distribution, percentage of egg reduction and clinical improvement rates in Iraq have been fully covered and discussed previously.

Methods

Review of previous work in Iraq

In 1970 Halawani & Baquir (1973a) tried Etrenol in the treatment of *Schistosoma haematobium* infections affecting 82 school children. The treatment was applied three months before the onset of the transmission season. The cure rate three months after treatment was found to be 58% of 71 cases. The low rate of cure, as compared to higher rates reported by other workers, is probably due to more rapid excretion of the drug by children than by adults, and also to heavy infection as well as lack of immunity.

The clinical improvement rate six months after treatment was judged by the

disappearance or marked decrease of haematuria and dysuria, recovery of physical fitness, increase in body weight and improvement in intellectual power. Of the children treated, 75% improved clinically six months after treatment; a 93% reduction occurred in the number of live eggs three months after treatment.

Shukri & Baquir (1973) showed that although the difference between the means of the levels of transaminases in the 5-10 year and 11-18 year age groups in the case of SGOT (serum glutamic oxalacetic transaminase) and in the age group of 5-10 years in the case of SGPT (serum glutamic pyruvic transaminase) were statistically significant, the writers believed that this could be due to the damage produced in the muscular tissue at the site of injection. The bilirubin value remained within normal limits in all of the 82 cases, with one exception. Halawani & Baquir (1973b) made a further trial with Etrenol where a second treatment was given one year after the first treatment to those school children who had remained positive in the first trial or had relapsed or had become reinfected after the initial treatment. The cure rate among re-treated cases was 57%, two months after treatment. Side effects after the second treatment were not serious. The clinical improvement rate was very marked (69%) three months after re-treatment.

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It is to be noted that in Iraq the cure rate was higher in adolescents than in young school children. The reasons are thought to be that adults have acquired a considerable degree of immunity which reinforces the action of schistosomicides, and also that they are less exposed to reinfection than are children.

The worm burden and number of ova excreted decrease with age in the adult host who is not regularly reinfected, whereas children in rural areas are exposed repeatedly throughout the transmission season. The cure rate may appear to be reduced at one and two months after treatment by the appearance of worms which were immature at the time of treatment (pretreatment infection). Also new infections acquired shortly before or after treatment may appear 45-90 days later. If treatment has been spread over the period of active transmission, the new infections may accumulate as the trial progresses. Evaluation must therefore be related to opportunity for reinfection. A very important consideration is the fact that the younger children have acquired very little immunity and worms which spontaneously die are being replaced by continuous exposure, so that the intensity of infection is being sustained at a high level between the ages of 5 and 15 years or actually increases during those years. Because of the low level of supporting immunity, the results show the direct unmodified toxic effects of the drug on the worm. This condition can be compared with the mathematical model shown in Table 12 (Dennis, 1972, pers. comm.). We have to reiterate that one injection of Hycanthonc constitutes a one-dose treatment but not necessarily one-dose cure in children. The idealised effects of treatment and re-treatment are illustrated in this same table, where it is estimated that the optimum tolerated dose (for the pa-

tient) is an L.D. 70 toxic dose for the female worm. Thus it is essential for control purposes to sustain the attack by re-treating at three months intervals, with survey and treatment at the end of the transmission season instead of just prior to the season. This information is of great value for the planning of any control programme based on chemotherapy. The incubation period for *S. haematobium* in humans is variable, it may be as short as six weeks or more than 12 weeks. Therefore actual transmission precedes the appearance of ova in the urine by an average of about two months, and this time factor must be taken in consideration when evaluating antibilharzial drugs. It is now generally accepted that a three months follow up period is optimal for evaluation in Iraq, whereas it is not so in areas where transmission is continuous throughout the year. Thus the season when the patients are treated and the interval between successive treatments are very important.

Area

Three primary schools, Ajyal, Abdul Wahab and Ossama schools, were selected in a new settlement, the so-called «labour area» which lies close to the highway leading to the new airport of Baghdad (at a distance of about 15 km from the centre of Baghdad). It is a new residential area for government labourers. Several years ago it was an irrigation area close to the suburbs of Baghdad. But it has greatly changed after the construction of the new Baghdad airport, when the main highway crossed the area and connected it with the centre of the town. The area is irrigated by canals No. 6 and No. 7, which has five branches. Both canals take water from Abu Ghraib canal, which in turn takes its water from the Euphrates River.

A total of 2117 school children, all boys, aged from 6-15 years, from those three schools, were studied in the school year 1972-1973 and were followed up. Of the 309 cases (14.6%) found infected, 285 were subjected to periodic treatment with Etrenol, as explained. The dosage used was 3 mg/kg body weight and treatment was given on an ambulatory basis in near by dispensaries.

Plan of operation

1. The initial injection is administered eight weeks after the end of the active transmission season, so that the maturation of worms which were immature at the time of treatment should not mask the initial curative action of the drug. This time falls in November in the Baghdad area.
2. The second essential requirement is to make the follow up examination 11-13 weeks after and to re-treat immediately all those who are still excreting viable ova ; this applies to February in the Baghdad area.

3. The next follow up should again be about three months later (May) and again all those still positive should be re-treated.
4. The next follow-up period (resurvey) should be at the end of the transmission season (October), i.e. at the start of the next school year.

This examination should include all those who were treated or re-treated and a significant sample of children who were negative a year earlier. This October examination should make it possible to identify the reinfections and these plus the new cases among those who were negative a year earlier (converted) would indicate the transmission rate. The trial is to be done on an out-patient basis.

Results and Discussion

Table 1 shows dates of periodic treatments for each school involved in the trial.

TABLE 1. Date of Hycanthone treatments in three primary schools in the Labour District, Baghdad.

Groups	Treatment							
	1st		2nd		3rd		4th	
Ajyal	Early Dec.	72	Late Feb.	73	Early May	73	Early Nov.	73
Abdul Wahab	Late Dec.	72	Early March	73	Mid-May	73	Mid-Nov.	73
Ossama	Early Jan.	73	Late March	73	Late May	73	Late Nov.	73

Table 2a, b, c, d shows the efficacy of Hycanthone against urinary bilharziasis as illustrated by the cure rates after periodic treatments of the school children for each school separately and for the whole group of the trial.

As seen from Table 2d, the overall cure rate 3 months after the first treat-

ment was 63% ; that 3 months after the second treatment was 35%, with a cumulative cure rate of 77%. The cure rate three months after the third treatment was 58% with a cumulative cure rate of 90%, and the cure rate 3 months after the fourth treatment was 45% with a cumulative cure rate of 95%.

TABLE 2. Efficacy of hycanthone mesylate against *Schistosoma haematobium* in Iraq. Cases still positive 3 months after treatment were re-treated. Dose 3.0 mg/kg, intra-musc.

Treatment	No. of School-children treated	Absent	Number examined	3-month follow-up examinations for viable ova					
				Positive		Negative		Cumulative negative	
				No.	%	No.	%	No.	%
a. Ajyal school									
1st	109	4	105	43	41	62	59	62/105	59
2nd	42	4	38	27	70	11	30	73/101	73
3rd	27	7	20	6	30	14	70	87/94	93
4th	4	1	3	1	34	2	66	89/93	96
b. Abdul Wahab school									
1st	21	1	20	10	50	10	50	10/20	50
2nd	10	3	7	3	43	4	57	14/17	82
3rd	3	1	2	2	100	0	0	14/17	82
4th	2	0	2	1	50	1	50	15/17	88
c. Ossama school									
1st	155	1	154	51	34	103	66	103/154	66
2nd	49	8	41	27	66	14	34	117/146	80
3rd	27	16	11	6	55	5	45	122/130	90
4th	6	0	6	4	66	2	34	124/130	91
d. Total 3 schools									
1st	285	6	279	104	37	175	63	175/279	63
2nd	101	15	86	57	65	29	35	204/264	77
3rd	57	24	33	14	42	19	58	223/240	90
4th	12	1	11	6	55	5	45	228/239	95

Table 3 shows the decline in prevalence per class (age group) in the 3 schools studied, comparing the school years 1972-1973 and 1973-1974; we note that among 2117 school children examined at the start of the former school year 309 school children were infected (14.6%), whereas at the start of the latter school year, among 2368 school children examined, only 93 school children were infected (3.9%). We also note a marked reduction

in prevalence as to class, especially in the classes for very young age groups. As a result of the decline in prevalence and of the marked reduction in cure rates, the socio-economic impact in such an area will be affected (Fenwick, 1971), i.e. the infected cases that are treated become more productive than those that are not treated, and infected persons show a lesser productivity than the non-infected persons.

TABLE 3. Percentage of bilharziasis infection in the classes of the 3 primary schools in the Labour District, Baghdad, for 2 school years.

Class	No. exam.		Infected			
			Number		%	
	72 — 73	73 — 74	72 — 73	73 — 74	72 — 73	73 — 74
1st	452	562	30	16	6.6	2.8
2nd	486	475	54	21	11.1	4.4
3rd	408	415	64	15	15.6	3.6
4th	279	396	54	9	19.3	2.2
5th	308	316	72	22	23.3	7.0
6th	184	204	35	10	19.0	4.9
Total for 3 schools	2,117	2,368	309	93	14.6	3.9

Table 4 shows the same decline in the prevalence of infection, but according to schools separately.

Table 5 gives an analysis of various epidemiological points for the three schools. We note that among the 93 cases found positive in October 1973, 45 were new cases altogether, as the pupils had not been present in October 1972; 22 cases represent a conversion of cases that had been negative in the previous year; 12 cases had either become reinfected or had relapsed and only 14 cases represent-

ed a failure of cure after the periodic treatment programme.

Table 6 shows further epidemiological data in the three schools 12 months after the first treatment. In the three schools of the trial, as a whole, the reinfection rate was found to be 9%, the incidence rate 1% and the transmission rate 10%. Whereas the snail density had been very high in the summer of 1972 before the trial, a snail survey in the summer of 1973 revealed no *Bulinus truncatus* which presumably were present only in a few residual pockets.

TABLE 4. Percentage of bilharziasis infection in the 3 primary schools in the Labour District, Baghdad, for the years 1972 and 1973.

School	Numbers						% infected	
	Examined		Infected		Negative		72-73	73-74
	72-73	73-74	72-73	73-74	72-73	73-74		
Ajyal	661	924	120	43	541	881	18.2	4.6
Abdul Wahab	729	880	24	18	705	862	3.3	2
Ossama	727	564	165	32	562	632	22.7	5.6
Total for schools	2,117	2,368	309	93	1,808	2,275	14.6	3.9

TABLE 5. Analysis of positive cases, 12 months after the 1st injection. (First resurvey in the school year 1973-1974)

School	Pupils not present in preceding school year	Present in preceding school year			Total No. of positive cases in Oct. 1973
		Negative	Positive		
			Re-infection or relapse	Failure of cure	
Ajyal	26	5	6	6	43
Abdul Wahab	4	10	2	2	18
Ossama	15	7	4	6	32
Total for schoos	45	22	12	14	93

TABLE 6. Some epidemiological data* concerning the 3 primary schools in the labour district of Baghdad, 12 months after first injection.

Schools	Reinfection rate %	Incidence rate %	Transmission rate %
Ajyal	11	1	12
Abdul Wahab	14	1	15
Ossama	6	1	7
Total for 3 schools	9	1	10

* Vector snails presumably present in a few pockets in nearby canals.

Our data (part of which are given in Table 4) show that the percentage of decline of prevalence was 66%, 75% and 39% in Ajyal, Ossama and Abdul Wahab schools respectively. The transmission rate (Table 6) was 15% in Abul Wahab school, which is higher than in the other two schools where it was 12% and 7%. We can thus say that the transmission rate is inversely proportional to the percentage of prevalence decline (deficit) for the two school years.

As in other rural areas in Iraq the transmission season is only during the summer months (May till September), and it is known (El Gindy et al., 1966) that it is best to apply molluscicides in June and to re-apply in September.

Table 7 shows that the cumulative cure rate was 95% 15 months after the first injection and that the average number of injections per cure was two.

TABLE 7. Analysis of treated cases in the trial as related to the number of injections and to cure.

No. of cases receiving at least:		
1 dose		285
2 doses		101
3 doses		51
4 doses		12
Total No. of treatments		455
No. of cases lost due to absenteeism		46
No. of cases cured		228
No. of cases cured / No. of cases treated	228	228
	285-46	239
Cumulative cure rate		95%
Average No. of injections per cure	455	2.0
	228	

As seen in Tables 8 and 9, the first and second urine re-surveys (12 and 15 months after the first injection respectively) show that the percentages of negative cases were 83% and 82% respectively.

Table 10 analyses the negative cases in the second urine re-survey (made 15 months after the first injection) as related to the number of courses received. We note that 72% of the negative cases had received only one injection, and hence we can conclude that in the presence of light infections and successful snail control, i.e. with no chances of reinfection, one course of injection is enough to achieve cure.

Table 11 on the other hand is an analysis of the positive cases at the second urine re-survey (performed 15 months after the first injection) as related to the number of courses received. We note that 50% of the positive cases received one or two injections, whereas the remaining 50% received three or four injections. We think that the explanation for this is the fact that the first half of the positive cases were originally mild cases with light infection who were exposed later to the risk of reinfection, whereas the second half of positive cases were severe cases with heavy infections who received multiple periodic injections (3 or 4) but still failed to be cured due to reinfection or relapse.

TABLE 8. First resurvey of all cases of the trial, one year after the first injection.

School	Numbers					
	Originally treated	Absent	Examined	(-) f. living ova	(+) f. living ova	(%) (-)
Ajyal	109	34	75	63	12	84
Abdul Wahab	21	8	13	9	4	70
Ossama	155	94	61	51	10	84
Total	285	136	149	123	26	83

TABLE 9. Second resurvey of all cases of the trial, 15 months after the first injection.

School	Numbers					
	Originally treated	Absent	Examined	(-) f. living ova	(+) f. living ova	% (-)
Ajyal	109	33	76	58	18	77
Abdul Wahab	21	8	13	9	4	70
Ossama	155	66	89	77	12	87
Total	285	107	178	144	34	82

TABLE 10. Analysis of the negative cases 15 months after the first injection as related to number of injections received.

School	Injections received								Total negatives	
	1		2		3		4			
	No.	%	No.	%	No.	%	No.	%	No.	%
Ajyal	40	69	8	14	8	14	2	3	58	100
Abdul Wahab	6	67	2	22	0	0	1	11	9	100
Ossama	58	75	9	12	8	10	2	3	77	100
Total	104	72	19	13	16	11	5	4	144	100

TABLE 11. Analysis of the positive cases 15 months after the first injection as related to number of injections received.

School	Injections received								Total positives	
	1		2		3		4			
	No.	%	No.	%	No.	%	No.	%	No.	%
Ajyal	5	28	3	17	9	50	1	5	18	100
Abdul Wahab	1	25	2	50	0	0	1	25	4	100
Ossama	5	42	1	8	3	25	3	25	12	100
Total	11	32	6	18	12	35	5	15	34	100

Dennis (1972) mentioned that a certain number of relapses do occur because of the survival and recovery of a few worms, as presented in Table 12. This is a matter of statistical distribution in

worm mortality and not a matter of resistance, i.e. it may happen that the patients who are still positive after three months had more worms initially and therefore more survivors.

TABLE 12. Theoretical effect of sequential treatment on population of female worms and egg production with dose administered being LD 70 for worms (after Dennis, pers. comm. 1972).

Treatment number	Number of adult female worms	Effect of dose		Daily output of viable ova per worm 3 mos. post-treatment	Total output of ova per host	Therapeutic result
		Worms killed	Worms survived (average)			
Pre-treatment	100	—	—	300	30,000	—
1	100	70% = 70	30	300	9,000	Improved, but no cured
2	30	70% = 21 ± S.E.	9	300	2,700	"
3	9	70% = 6.3 ± S.E.	3	300	900	"
4	3	70% = 2.1 ± S.E.	1	300	300	"
5	1	70% = 0.7 ± S.E.	0	0	0	"

Note: In this over-simplified model it is assumed that all surviving female worms are able to find a surviving male and return to the vesical plexus within 3 months to renew egg production at the normal rate, and that immunity does not affect survival rates. Patients males are more susceptible to Hycanthone than females, so that the effect of treatment on egg production is enhanced, and tissue resistance will further reduce survival by destroying damaged worms.

As regards side effects, all treated cases tolerated the drug well. Side effects were mild or moderate and hospitalisation was not needed in any of the treated cases, which were all treated on an ambulatory basis.

Ruas (1971) in Mozambique treated 1,000 cases of all ages with Etrenol at a dosage of 3-3.5 mg/kg b.w. on a basis of periodic treatment every two months for those still positive. The overall cure rate was about 90% and the cumulative cure rate two months after the fourth treatment was 99%. Saif et al. (1971) in Egypt treated 550 cases and obtained a cure rate of 66.7% after three months (367 cases were cured and 185 cases were yet positive, of which 132 were re-treated, with a cumulative cure rate of 81.6%. Resurvey at the end of the year showed 101 failures, 161 reinfections and 115 new cases). In an evaluation of anti-bilharzial drugs in Tanzania (Fenwick, 1971; Fenwick & Jorgenson, 1973), it was demonstrated, after the treatment of 1922 cases of *S. mansoni* of all ages, that Hycanthon was more efficient in children than Niridazole (Ambilhar), curing 68% as against 36%. The overall cure rate was 72% for Hycanthon and 59% for Niridazole.

Recent WHO reports on chemotherapy with Etrenol (WHO, 1972a,b) made it clear that Etrenol, like all other anti-bilharzial drugs, is a potentially toxic drug and that it needs medical supervision in selective mass treatment campaigns. Dennis (1973) mentioned that Etrenol is not a hepatotoxic drug.

Finally we wish to mention here that the programmes of the mass treatment campaigns in Iraq (Baquir, 1975) were planned and implemented in accordance with the remarks made in the present paper.

Summary and Conclusions

Sequential treatment was given to 285 school children at a dose of 3.0 mg/kg body weight. Re-examination was carried out at three months post-treatment and those still positive were scheduled for re-treatment. The cumulative cure rate 15 months after the first treatment was 95%. The average number of injections per cure was two.

Prevalence in school children was reduced from 14.6% to 3.9% in the presence of an active transmission rate of 12% (based on children originally negative but converted to positive during the year).

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**A PRELIMINARY REPORT ON SCHISTOSOMIASIS CONTROL BY
CHEMOTHERAPY IN MARQUIS VALLEY, ST. LUCIA, WEST INDIES**

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In the Marquis Valley area of St. Lucia, treatment of all persons found infected with *Schistosoma mansoni* has been carried out in an effort to stop transmission of the disease. Stool examinations were carried out on the population of approximately 3,100 annually in late 1971, 1972 and 1973 to provide precontrol baseline data.

In February and March, 1974, treatment was offered to all found infected at the time of the 1973 survey. The treatment used was a single injection of hycanthone, 2.5 mg/kg body weight. Patients were treated at the local health center after a brief history and physical examination. Pregnant females were excluded and patients with hepatosplenomegaly or other chronic diseases were brought to the hospital ward for treatment. A nurse called on all treated patients daily at their home until no side effects were reported.

Of 677 patients who received hycanthone, 22.8% vomited during the first 24 hr but 44.5% had no side effects. While such a rate of vomiting is undesirable, it did not materially affect cooperation in the treatment programme. It is relevant that most side effects occurred only during the first 24 hr after treatment. On day two, 94% reported no side effect; on day three, 99%. The pain noted

at the site of injection was mild and there were no cases of jaundice.

The population was re-examined after treatment in late 1974. Of 160 found infected, only five were verified treatment failures. Nine infected persons had moved or returned to the valley in the past year and five had not previously been examined. Of the remaining apparent new infections, 103 of 141 had previously had a positive stool examination in 1971 or 1972 and therefore could represent old light infections. Of the 38 whose stools were positive for the first time in 1974 only 14 were under age 15. Because of the difficulty in detecting infection with a single stool examination, especially when both prevalence and intensity of infection (egg excretion) is low, it is these 14 patients who are most likely to represent infections acquired since the institution of control measures.

Treatment was carried out for the second time during the course of the 1974 follow-up survey and 156 persons were treated with hycanthone, again at 2.5 mg/kg body weight. Side effects were very similar to those of the first treatment; 35.7% had no complaint; 21.2% vomited.

In the first follow-up examination after treatment the villages were grouped into high and low transmission areas,

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based on whether precontrol incidence between 1972 and 1973 was more or less than 20%. The overall reduction in prevalence was from 25% in 1973 to 7% in 1974. However, since chemotherapy is bound to directly affect prevalence, the only measure of effectiveness of the control of transmission, is incidence, or the rate of new infections.

There was significant reduction in incidence of new infections in both high and low transmission areas one year after treatment. The total incidence in 0-14 year olds has fallen from 11.8% in 1972-73 to 5.1% for 1973-74. The true incidence is, however, lower since, as previously described, more than half of these apparent new cases had had a positive stool in 1971 or 72.

An estimate of the possible effects of a chemotherapy control programme in Marquis valley was made before the campaign. This estimate was based on a single stool examination, a 90% acceptance of treatment and a 95% reduction in egg excretion of those treated. Provided all persons submitted a stool sample, we estimated that the community egg excretion

or contamination potential would be reduced by 66% by the initial treatment. In actual fact we obtained a 63% reduction — in other words the potential contamination of rivers and streams with *S. mansoni* eggs was reduced by 63%. No naturally infected snails have been found in the area since chemotherapy started and sentinel snails have not become infected.

The cost of this control programme was U.S. \$ 4224.00 in the first year and \$ 2500.00 in the second. The cost of fecal examination (72c. per specimen) makes up a large part of the cost and is proportionately greater in the second year when fewer people required treatment. The cost per person protected in the control scheme area was \$ 1.34 in the first year and 0.81 in the second. The cost per treatment was \$ 1.75.

In summary we feel that the results at one year after a chemotherapy programme to control schistosomiasis are encouraging and continued treatment and follow-up may show it to be an effective method of control.

HYCANTHONE REGIMES IN URINARY SCHISTOSOMIASIS

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Trials with hycanthone against schistosomiasis in Tanzania have been reported by McMahon & Samatta (1968, 1969), McMahon (1969, 1974), Bailey (1970), Davis et al. (1971), Jorgensen et al. (1970) and Eyakuze & Rugemalila (1974).

Because hycanthone in a dose of 3 mg/kg of body weight induced severe vomiting in a proportion of persons (6%) with *Schistosoma mansoni* infections, McMahon (1969) considered that this dosage regime should not be used in mass chemotherapy against this parasite in East Africa and Bailey (1970), following the treatment of urinary schistosomiasis with the same dose, considered that the use of hycanthone for mass treatment in virtually uncontrolled situations could not yet be recommended.

In Uganda, Ongom (1970) used 3 mg/kg against *S. mansoni* and considered further trials were indicated in order to find the optimum dosage. In Kenya, Rees et al. (1974) reported a favourable parasitological response against *S. mansoni* with a single dose of hycanthone (1.5 mg/kg). This dosage was considered to be acceptable and safe.

Following the report by an 'Expert Committee on Schistosomiasis Control' (WHO, 1973) and earlier recommendations of two WHO 'Consultant Groups' (1972) on the need for adequately con-

trolled comparative field trials of schistosomicides in a single endemic area, trials were commenced at Tanga on persons (schoolchildren) with urinary schistosomiasis with the following objectives:

- 1) To compare niridazole (single oral dose 35 mg/kg per day for five days) with hycanthone in a single intramuscular dose of 2.5 mg/kg.
- 2) To see if splitting the 2.5 mg/kg dose of hycanthone into doses of 1.25 mg/kg given one week apart reduced the incidence of side effects and maintained the parasitological response.
- 3) To give more precise information on side effects and the parasitological response by designing double blind trials using a placebo and various dosage regimes of hycanthone (1.5, 1.75 and 2.5 mg/kg).

Materials and Methods

Series 1

An investigation was made of niridazole in a single daily dose of 35 mg/kg for five days and of hycanthone at 2.5 mg/kg in a single intramuscular injection and in a split dose of 1.25 mg/kg given one week apart.

After the screening of male pupils (aged 8-15 years) at a rural school, more

than 150 positive cases were randomly allocated to three different treatment groups :

Group A received the single dose of hycanthone. Group B the split dose of hycanthone and Group C received niridazole.

Apart from standard procedures adopted in clinical trials the following aspects of methodology were emphasized :

1) Parasitological examinations were conducted before treatment and 2, 4, 6, 12, 24 and 30 months after treatment. At each examination urine specimens were collected between 10 a.m. and 12 noon on two consecutive days. Following sedimentation the mean egg load of a 10 ml sample was estimated, using the method described by Davis (1966) in which both hatched miracidia and non-viable eggs were counted.

2) Drug efficacy was estimated by calculating both cure rates and percentage reduction in egg excretion.

3) Observer variability, both intra and inter-variation of the examining technicians, was investigated.

4) Built-in controls: In order to improve reliability of data from laboratory examinations a blind reading was built in; according to a code 20% of readings were checked by another observer. Follow-up examinations were organised in such a manner that technicians did not know the correct group of persons providing specimens.

Series 2

This series included two double blind comparative trials: (1) hycanthone at 2.5 mg/kg and placebo to boys. (2) hycanthone at 1.5 and 1.75 mg/kg and placebo to girls.

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Technical procedures were essentially the same as in Series 1. The placebo was the same colour and consistency as the active drug. The total number of pupils treated was 130.

In order to evaluate side effects, a questionnaire was prepared on which general (unsolicited) complaints were recorded as well as complaints that were solicited specifically. Pupils absent from school the day after treatment were also recorded.

Results

1. *Comparative trial with niridazole 35 mg/kg/5 days and hycanthone 2.5 mg/kg single dose and split dose given 1 week apart*

The results of the early follow-up examinations (2-4 months) are shown in Table 1.

At the two-month follow-up the difference in apparent cure rate observed between the niridazole group (Group C) and the group given a single dose of hycanthone 2.5 mg/kg (Group A) is not statistically significant ($X^2 = 1.96$). Both regimes showed a percentage reduction in egg counts of 96% in non-cured persons. Although an analysis of heavy infections only (egg loads 500) shows niridazole to have a higher cure rate (Table 2), there is no significant difference between the two regimes ($P > .05$).

On the other hand the group given the split dose of hycanthone (B) showed a cure rate of 18.2% at two months (Table 1) and reduction in egg load was also poor (71.2%) compared to the other two groups.

Long-term follow-up results (6-30 months) are shown in Table 3.

TABLE 1. Apparent cure rates in comparative trial with Niridazole 35 mg/kg/5 days and hycanthone in a single dose 2.5 mg/kg and two doses each 1.25 mg/kg given 1 week apart, two and four months after treatment.

	Examination	Group A Hycanthone single dose	Group B Hycanthone split dose	Group C Niridazole
Number examined	Pre-treatment	51	47	50
	2 mth follow-up	46	44	46
	4 mth follow-up	49	43	47
Apparent cure-rate (%)	2 mth follow-up	56.5	18.2	61.1
	4 mth follow-up	46.9	18.6	62.2
Geometric mean egg-count	Pre-treatment	255.3	207.6	209.0
	2 mth follow-up	14.8	48.6	38.0
	4 mth follow-up	28.3	56.6	47.0
95% Confidence limits of mean	pre-treatment	159.4-409.0	126.1-341.8	127.4-342.8
		7.6-28.6	27.7- 85.3	12.8-111.2
		16.4- 48.9	30.3-105.9	16.9-130.7

TABLE 2. Results in heavy infections (egg load = 500/10 ml) four months after treatment with niridazole and hycanthone.

Drug	Pretreat- ment egg load	Cure rate	Percentage reduction in egg load
Hycanthone 2.5 mg/kg single dose	1390.9	4/18 (22.2%)	99.4%
Niridazole 35 mg/kg/5days	1263.8	10/17 (58.8%)	99.8%

TABLE 3. Long term follow-up examinations of comparative trial with hycanthone and niridazole in persons re-exposed to *S. haematobium* infections.

Drug	Follow-up examinations											
	6 months			12 months			24 months			30 months		
	Cure rate % age	Mean egg load	% age mean egg reduct.	Cure rate % age	Mean egg load	% age Mean egg reduct.	Cure rate % age	Mean egg load	% age mean egg reduct.	Cure rate % age	Mean egg load	% age mean egg reduct.
A. Hycanthone . 2.5 mg/kg single dose	21/44 (47.7%)	51.5	79.8%	18/36 (50%)	169.1	33.8%	7/22 (31.8%)	123	51.8%	8/19 (42.1%)	220	13.8%
B. Hycanthone, split dose each of 1.25 mg/kg 1 week apart	12/46 (26.1%)	66	68.2%	5/30 (16.7%)	144.2	30.5%	5/28 (17.7%)	205.9	0.8%	6/22 (27.3%)	133.5	35.7%
C. Niridazole 35mg/kg/5days	23/45 (51.1%)	26.4	87.3%	18/39 (46.1%)	32	84.7%	11/23 (47.8%)	112.7	46.1%	8/18 (44.4%)	60.4	71.1%

Side effects among children of Group B (split hycanthone dose) were insignificant. Minor side effects — headache, dizziness, nausea and abdominal pain — were much more common in the niridazole group (C) than the other two groups. However, there were no major side effects with niridazole. But the incidence of vomiting was greater among the single dose hycanthone group (A) and in two persons vomiting was excessive and severe.

2. *Double blind trials with hycanthone :*
(a) *with a dose of 2.5 mg/kg and a placebo ; (b) with single dose of hycanthone 1.5 and 1.75 mg/kg and a placebo (Table 4)*

The difference in egg output reduction achieved by giving hycanthone in a dose of 2.5 mg/kg instead of 1.5 or 1.75 mg/kg is highly significant ($t = 84.0$ and 20.8 respectively at two months). The higher cure rate after 1.5 mg/kg compared to 1.75 mg/kg is due to the larger number of light infections in the former group. At four months the egg count of the group given 1.5 mg/kg is increased considerably.

The maintenance of egg reduction over 24-30 months is demonstrated in all treated groups (Tables 3, 4). But the control group (Table 4) also shows a substantial reduction in egg output throughout this period.

The results of a study of drug reactions are shown in Table 5. Side effects with dosage regimes of 1.5 and 1.75 mg/kg hycanthone are minor. Complaints are much more common with 2.5 mg/kg hycanthone compared to the placebo ($t = 2.39$) with vomiting being the most important drug reaction.

Discussion

In the present trials parasitological results from a course of niridazole at 35 mg/kg for five days and a single dose of hycanthone at 2.5 mg/kg were equivalent.

Both these regimes have disadvantages for control schemes : hycanthone may produce severe vomiting and niridazole may result in a high default rate.

Splitting the 2.5 mg/kg dose of hycanthone into two doses given one week apart results in a decreased incidence of side effects, but the parasitological response is also substantially reduced and this regime is not recommended.

Although the lower single doses of hycanthone (1.5 and 1.75 mg/kg) produced only minor side effects, the difference in egg output reduction achieved by giving hycanthone in a dose of 2.5 mg/kg instead of 1.5 or 1.75 mg/kg is highly significant.

Following investigations at Tanga, Davis (personal comm.) considered a dose of 2.0 mg/kg to be too low, less than half of the persons given this dose being classified as cured. Dennis & Kobus (1971) also noted that efficacy in urinary schistosomiasis is less reliable at 2.0 mg/kg than at higher doses. Thus a dosage of 2.0 mg/kg or below gives a low cure rate, a dosage of 2.5 mg/kg or above has too high an incidence of side effects, hence the dosage suggested as a result of these trials would be within this range.

The cumulative effects of sequential re-treatment in urinary schistosomiasis was investigated by Saif et al. (1971). Using doses of 3 mg/kg these authors retreated residual positives three months after the first dose and examined again three months after the second dose. The cure rates were nearly the same (67% and 62%). The cumulative cure rate for the two doses was 82%.

TABLE 4. Trials with hycanthone (1.5, 1.75, 2.5 mg/kg of body weight) in *Schistosoma haematobium* infections in school pupils re-exposed to infection.

Dose	Pre-treatment	Follow-up examinations											
		2 months			4 months			6 months			15 months		
	Mean Pre-treatment egg load +	Cure rate	Mean egg load*	% age mean egg reduct.	Cure rate	Mean egg load	% age mean egg reduct.	Cure rate	Mean egg load	% age mean egg reduct.	Cure rate	Mean egg load	% age mean egg reduct.
1.5mg/kg	153.9	13/30 (43.3%)	17.4	88.7	11/29 (37.9%)	30.9	79.9	10/27 (39%)	29.0	81.2	14/25 (56%)	8.10	94.7
1.75mg/kg	411.1	8/29 (27.6%)	13.8	96.9	7/29 (24.1%)	28.3	93.1	6/27 (22.2%)	47.8	88.4	7/28 (25%)	16.41	96.1
Placebo	321.1	Nil	157.8	50.8	Nil	161.5	49.8	1/28 (3.5%)	165.0	48.7	2/23 (8.7%)	50.5	84.3
2.5mg/kg	269.8	15/17 (88.2%)	3.3	98.8	12/16 (75%)	2.3	99.2	Not examined	5/10 (50%)	87.9	4/9 (44.4%)	32.65	87.9
Placebo	329.9	0/17	186.2	43.6	0/17	213.2	35.4	0/12	338	2.4 increase	0/8	78.6	76.2
												80.3	75.7

+ Geometric mean

* Non cured persons.

TABLE 5. Side effects with hycanthone at dosages of 2.5, 1.75 and 1.5 mg/kg.

Regime	No. treated	Absent from school day after inj.	Spontaneous complaints	Response to specific questioning								Remarks
				Anorexia	Nausea	Vomiting	Abd. pain	Pain inj. site	Headache	Dizziness	Weakness	
Placebo	18	3	Dizziness (2) Abdominal pain (2) Fever (2)	1	1	—	4	2	2	3	4	
2.5 mg/kg	20	3	Nausea (1) Dizziness (1) Abdominal pain (2) Vomiting (5) Pain inj. site (2) Fever (1)	3	7	8	3	4	3	3	4	In one person vomiting was severe.
Placebo	30	2	Dizziness (2) Headache (3) Abdominal pain (1) Dizziness (2) Fever (3)	2	4	1	4	2	7	3	7	
Hycanthone 1.5 mg/kg	30	3	Headache (1) Nausea (1) Abdominal pain (3) Vomiting (2)	1	4	3	9	7	5	4	4	Although there was mild irritation at injection sites no lumps occurred.
1.75 mg/kg	30	2	Nausea (4)	3	7	3	5	11	3	3	6	

In the present trials a total of 34 persons classed as failed cures following the various hycanthone regimes used were re-treated with 1.5 mg/kg six months after the first treatment. Only eight were cured (23.5%) two months later, and egg excretion in the non-cured tended to remain high (McMahon, unpublished data).

Long-term follow-up results in the present work show that reinfection rates in persons cured at four months are low. In most cases egg excretion of non-cured persons remains well below pre-treatment levels.

Evidence was given by Cook et al. (1974) for *Schistosomiasis mansoni* that the excellent therapeutic effect of hycanthone following a dose of 3 mg/kg tends to remain fairly constant through two years after treatment. After treating *S. mansoni* and *S. haematobium* infections with niridazole, Abdallah & Saif (1969) noted no reinfections in persons who were examined 12 months after therapy and McMahon (1968) followed persons residing in an *S. mansoni* endemic area for 36 months after treatment with niridazole. There was no evidence that treatment had adversely effected the immune response of persons re-exposed to infection.

Although it is an advantage that hycanthone treatment tends to maintain, in the long term, the reduction of egg excretion which has been achieved, even though the cure rate with non-toxic dosage is not high, the trials demonstrate two important factors, which are often overlooked in the methodology of drug trials :

- 1) the importance of a control group when evaluating the results of long-term follow-up (Figs. 1, 2) ;
- 2) the effect on the parasitological response of the level of transmission in an endemic area at the time of the trial (Fig. 3, Tables 1, 2).

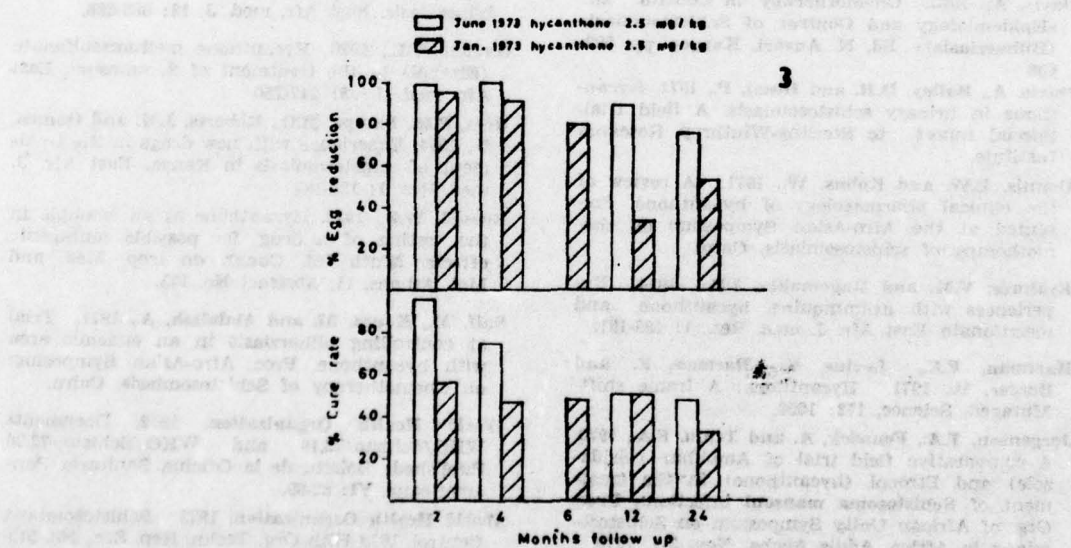
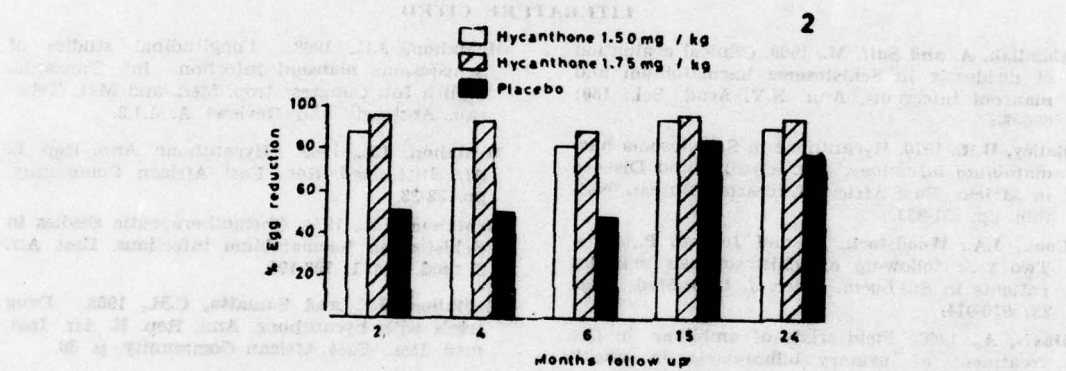
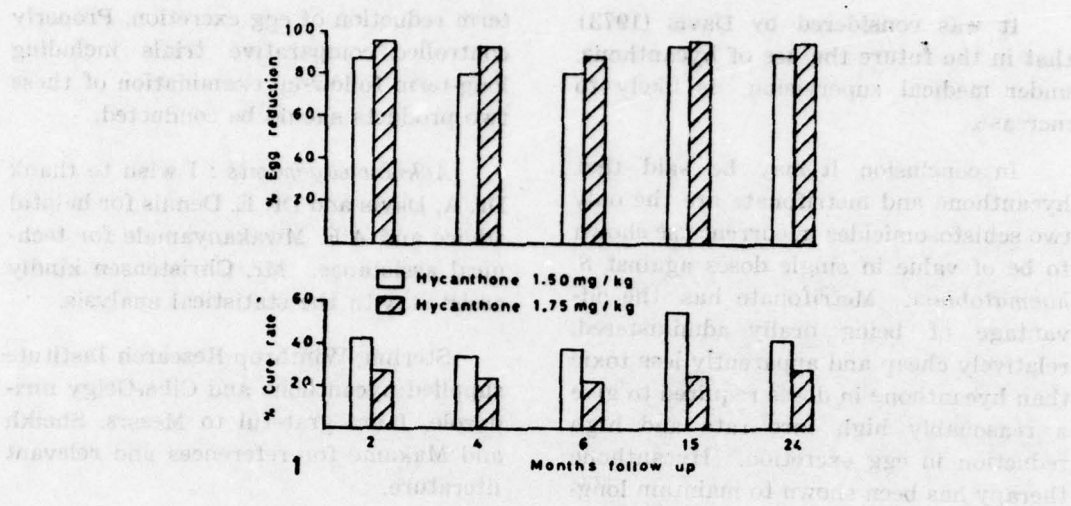
Although, in groups given the lower single doses of hycanthone (Table 2), the parasitological response remains favourable throughout, the placebo group also shows considerable egg reduction at the 15 and 24 months examinations. Two relatively dry seasons accompanied by lowered transmission could explain this phenomenon.

Despite similar mean pre-treatment egg levels, both the cure rate and maintenance of the therapeutic effectiveness of two single doses of 2.5 mg/kg of hycanthone differ (Tables 1 and 4). A major probable reason for these differences is that comparative trials shown in Table 1 were conducted just prior to the expected transmission season whereas trials in Table 2 commenced after the main transmission period.

Thus even when identical techniques are utilized for therapeutic evaluation of schistosomicides, comparative field trials should be concurrent and long-term follow-up results should include a control group.

Since the appearance of a report on mutagenicity of hycanthone in *Salmonella* spp. by Hartmann et al. (1971), there has been a controversy as to whether the drug will produce mutagenesis in mammalian germ cells. But Russell (1973) found no evidence of mutagenicity in offspring of male mice injected intraperitoneally with 150 mg/kg of hycanthone methanesulfonate.

The comparative risks involved in the administration of schistosomicides, including hycanthone, were studied by two WHO consultant Groups convened in 1971 and 1972. These reports were published (WHO, 1972). No evidence was found to justify a recommendation that the use of hycanthone for the treatment of schistosomiasis should cease.



It was considered by Davis (1973) that in the future the use of hycanthone, under medical supervision, is likely to increase.

In conclusion it may be said that hycanthone and metrifonate are the only two schistosomicides in current use shown to be of value in single doses against *S. haematobium*. Metrifonate has the advantage of being orally administered, relatively cheap and apparently less toxic than hycanthone in doses required to give a reasonably high cure rate and high reduction in egg excretion. Hycanthone therapy has been shown to maintain long-

term reduction of egg excretion. Properly controlled comparative trials including long-term follow-up examination of these two products should be conducted.

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**CLINICAL TRIAL WITH HYCANTHONE IN SCHISTOSOMA MANSONI
AND SCHISTOSOMA HAEMATOBIIUM INFECTIONS IN TANZANIA**

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Hycanthone (Etrenol), the hydroxymethyl metabolite of lucanthone was discovered and studied at the Sterling-Winthrop Research Institute by Rosi et al. (1965). It was reported to be a highly active antischistosomal agent when administered orally or intramuscularly in experimental infections with *S. mansoni* in mice and hamsters and has since been found to be effective against human infections of *S. mansoni* and *S. haematobium* by both the oral and intramuscular routes.

Hycanthone seems to accumulate in the gut of schistosomes and it is possible that the worms die due to damage to that organ (Olivier, 1969 ; Dennis, 1970).

Early clinical trials in South America were reported by Katz and Pellegrino (1967), Argento et al. (1967), Salgado et al. (1968), da Cunha and Cançado (1968) and Katz et al. (1968a,b).

Katz and his co-workers claimed that after oral administration of hycanthone approximately 80% of 52 patients were cured four months after treatment. The dose used in this trial was 2-3 mg/kg body weight per day, in two divided daily doses for five days. The side effects observed such as nausea, vomiting, vertigo and headache were considered by the authors to be of minor clinical significance.

In preliminary clinical trials a single injection of hycanthone sulfamate salt 3-4 mg/kg was considered to be highly effective by Pellegrino and Katz (1968).

A symposium about hycanthone was held during the Eighth International Congress of Tropical Medicine and Malaria in 1968.

In papers presented at this Congress, Katz et al. (1968b) considered hycanthone to be a powerful and safe antischistosomal agent, whereas Argento et al. (1967, 1968), although they considered hycanthone to be effective, adopted a slightly more cautious approach and noted that oral administration of the drug was accompanied by severe side effects.

Following further clinical trials, Katz et al. (1969) reported a 'cure rate' of 94% when 49 patients were treated with a single injection of 2-3 mg/kg of the methanesulphonate salt.

Very favourable reports on hycanthone came from Rhodesia (Clarke et al., 1969). These authors considered that, because of the high cure rate in both *S. mansoni* and *S. haematobium* infections achieved in their initial trials, plus the low incidence of side effects, hycanthone was likely to be highly suitable for mass chemotherapy.

Less favourable reports came from Egypt (Abdallah et al., 1969). These authors noted that orally administered hycanthone in doses of 2-4 mg/kg body weight daily for 3-5 days gave a high incidence of undesirable drug reactions.

Preliminary investigations using single intramuscular injections of hycanthone commenced in East Africa in 1968 were published by McMahon and Samatta (1968, 1969) and by McMahon (1969). It was stated that, although a critical evaluation of hycanthone must await a larger series of patients, vomiting (both the high rate and severity) would be a major disadvantage in mass chemotherapy at this dosage in East Africa.

The present clinical trials studied the effectiveness and toleration of a single intramuscular injection of hycanthone given to 71 persons with schistosomiasis.

Materials and Methods

Fifty-one persons with *S. mansoni* infections, eight with *S. haematobium* infections and four with mixed infections of both *S. haematobium* and *S. mansoni*, were given a single intramuscular injection of hycanthone methanesulphonate in a dose of 3 mg/kg of body weight. Deep intramuscular injections were given into the gluteus minimus. In addition to this main trial with a dose of 3 mg/kg a small number of persons, eight, were given other intramuscular dosage regimes of 2, 2.5 and 3.5 mg/kg.

S. mansoni infections were initially diagnosed by the A.M.S. III method (Hunter et al., 1948).

A number of persons were used as their own controls after the manner suggested by Davis (1966). In 20 patients (Group A), whole single specimens of stools were collected once weekly for four weeks prior to treatment. Specimens were thoroughly mixed, 5 g were carefully weighed and egg counts done using the modified Bell technique. Stools from another 12 patients (Group B), were examined on alternate days for five days. The results of these examinations are shown in Table 1.

Following the initial examinations, groups were divided into four categories according to egg load per gram of faeces; Group 1, 1-50; Group 2, 51-200; Group 3, 201-500; and Group 4, 501+.

Fluctuations were noted in the egg counts of various individuals* in subsequent examinations. These variations were insufficient in most cases to place the same person in different groups at different examinations. (A few exceptions were those on the borderline but after three or four examinations, they were categorized according to the mean reading).

In order to obtain information on the variation of egg counts in the different series of examinations, in Group A and B, an analysis of variance test was applied.

For Group A the variance ratio (F) is 0.18 with 3 and 76 degrees of freedom and F for Group B is 0.25 with 2 and 33 degrees of freedom. According to Fisher and Yates (1963, Table 5), both computed values of F are not significant, i.e. there is no significant difference between series.

* When examining egg excretion patterns, if marked variation exists between samples taken from the same person, it is important to know whether these variations are due to intrinsic variation in the sample itself or are due to inaccuracy and imprecision of the technique of measurement and to observer errors. But in the present instance, the main objective of these weekly and alternate day studies was to use persons as their own controls, so that any alteration in egg load following treatment could mainly be attributed to the drug being studied.

TABLE 1. Egg excretion pattern in persons with *Schistosoma mansoni* infections.

Group	Person No.	Examination			
		1st week	2nd week	3rd week	4th week
Group I 20 persons examined once weekly for 4 weeks	1	43	67	57	77
	2	190	197	195	210
	3	113	117	70	87
	4	7	13	7	10
	5	70	83	63	77
	6	20	23	13	17
	7	2140	2217	4990	650
	8	113	333	287	277
	9	523	357	387	307
	10	10	50	43	40
	11	100	110	130	100
	12	70	97	90	83
	13	30	23	27	20
	14	20	67	67	57
	15	293	310	233	240
	16	37	60	137	67
	17	87	103	77	60
	18	170	130	317	210
	19	10	10	13	10
	20	13	20	17	13
		1st day	3rd day	5th day	
Group II 12 persons examined on alternate days for 5 days	1	7	10	10	
	2	1383	907	1090	
	3	1857	1010	987	
	4	793	290	727	
	5	620	650	625	
	6	190	227	247	
	7	473	247	357	
	8	37	50	33	
	9	17	23	13	
	10	13	40	17	
	11	317	183	270	
	12	230	160	170	

Twenty-four hour collections of stools were obtained before, as well as two, four and six months after treatment, but in order that the same technique of examining stools of controls should continue to be used, an additional stool specimen was collected and examined by the modified Bell technique. In addition to the examination of all available persons at two, four and six months, some (16) were also

examined one month after treatment. Cures were considered to have occurred only when the A.M.S. III technique, a hatching test and the Bell method, used on a 24 hr specimen, were all negative.

The centrifuged deposits of 10 ml of midday specimens of urine were examined and *S. haematobium* ova, if present, were counted as described earlier.

Special investigations on 21 persons included routine urine examinations, haemoglobin estimation, total w.b.c. and differential counts. Fifteen subjects had electrocardiograms taken prior to, and the day following, therapy.

Results

- 1) Dosage regime 3 mg/kg body weight in a single intramuscular infection. Drug effectiveness.

— One month follow-up examination

Of the small numbers of persons examined 1 month after therapy, four of seven treated for *S. haematobium* infections were excreting no ova. All three methods used for stool examination were negative in seven of nine persons treated for *S. mansoni* infections. In the non-cured persons, a large reduction in egg output of both *S. mansoni* and *S. haematobium* ova had occurred.

— Two and four month follow-up examination

S. mansoni infections

The four groups roughly correspond to light, moderate, heavy and very heavy infections. Table 2 shows the cure rate and the mean percentage reduction in egg load in non-cured patients at the two and four month follow-up examinations.

Persons with light infections (Group 1) had much higher cure rates but much lower reduction in egg excretion, than did members of more heavily infected groups.

The t-test was used to compare the results obtained at the four month follow-up in a niridazole trial by McMahon and Kilala (1966) with those of the present trial. Patients in both trials were similar in age, intensity of infection and nutritional state and the same methods were used to evaluate drug effectiveness. Although conducted in different years, both

TABLE 2. Results of a trial with a single injection (3 mg/kg) of hycanthone methanesulphonate given to persons with *Schistosoma mansoni* infections.

Pretreatment egg load per g of stool	Two month follow-up			Four month follow-up		
	Cured Number	percentage	Mean reduction in egg load in uncured persons	Cured Number	percentage	Mean reduction in egg load in uncured persons
Group 1: 0-50 (light infections)	11/13*	84.6%	87.8%	6/10	60%	63.1%
Group 2: 51-200 (moderate infection)	11/15	73.3%	94.2%	3/15	20%	87.6%
Group 3: 201-500 (heavy infection)	3/8	37.5%	98.2%	3/8	37.5%	95.8%
Group 4: 500+ (very heavy infections)	0/5	0	99.1%	0/5	0	98.2%

* Numopator = number cured

Denominator = number examined

trials occurred at a similar period in the transmission season of years with similar rainfall. The difference in the results of the two trials are statistically insignificant at the 5% probability level.

In Table 3 persons in the present trials were divided according to age. The cure rates at 4 months, i.e. 0/3 (5-10 years), 0/7 (11-14 years), 4/10 (15-18 years) and (8/18 years +) suggest that adolescents and adults respond to treatment better than children.

TABLE 3. Cure rate of *Schistosoma mansoni* according to age.

Age in years	Cure at 2 months	Cure at four months
5 — 10	2/3	0/3
11 — 14	2/7	0/7
15 — 18	5/10	4/10
18 +	16/21	8/18

In the 5-14 age group 0/10 were cured. In order to confirm that the poorer response in children was related in some way to age, and not just to the presence of more of the heavy infections in the younger age groups, the pretreatment median egg load and the percentage reduction in egg excretion at four months was calculated for each group (Table 4).

TABLE 4. Percentage reduction in egg excretion four months after treatment for the different age groups.

	Age group (years)		
	5-14	15-18	18+
Pretreatment median (eggs/g)	121	230	53
Reduction at 4 months	92.3%	97.7%	99.7%

Although the median egg load was lower in the adult group (18 +) than in the group containing children, the percentage reduction in egg load was better in the former than the latter group (99.7% as compared to 92.3%). A distribution free test (Wilcoxon's rank order test) is significant at the 5% level. Although the pretreatment median egg load was higher in the adolescent (15-18 years) than in the group containing children, yet both the cure rate and the reduction in egg load was greater in the adolescent group. From these results, it can be concluded that factors other than just the intensity of infection are responsible for the poorer response of children to therapy than the other age groups.

Of 14 patients negative at the four-month examination, 13 were still negative at the six-month follow-up.

S. haematobium and mixed infections of both *S. mansoni* and *S. haematobium*

The results are shown in Table 5.

TABLE 5. Cure rates two months and four months after treatment.

Infections	2 months	4 months
<i>S. haematobium</i>	5/6	6/7
Mixed	4/4	3/3

The uncured *S. haematobium* case was a seven-year old girl who originally had a heavy infection (2997 ova/10 ml). At four months her egg load was reduced by 98.2%.

— Toleration

Nausea and vomiting were common side effects. Of the 63 persons given this drug regime, 25 (39.7%) vomited and of these, eight (12.7%) did so more than

twice. One vomited 11 times and three others between 6 and 10 times. Although vomiting tended to occur 4-8 hours after therapy, in some cases the onset was delayed. An adolescent girl and a young adult commenced vomiting 20 hr after treatment and vomited six and seven times respectively. In most cases, vomiting ceased without antiemetics being administered, but two persons who were vomiting excessively, were given an antiemetic.

The vomiting rate was higher in children than in adults. There was no difference in the rate of vomiting between persons with *S. mansoni* and *S. haematobium* infections.

A comparison of weights before and 24 hr after therapy showed a small decrease in most cases. But, persons with excessive vomiting tended to lose 2-3 kg.

Although the drug was essentially painless on injection, seven patients (11.1%) complained of tenderness at the injection site one to three days after therapy.

Drug reactions other than vomiting, were insignificant and the haematological and urine examinations revealed no adverse effects of therapy. Post treatment electrocardiograms showed no changes in pattern compared to the pretreatment ones. However, the post treatment electrocardiograms in the present series were taken 24-48 hr after therapy (our electrocardiographic machine was out of order at the one month follow-up). It is noted that Katz et al. (1968a) observed flattening of ST segments and T waves in 13 of 23 cases from one to four weeks after therapy. Salgado et al. (1968) considered that the electrocardiographic changes occurring subsequent to hycanthone treatment are only of minor importance.

2) Other dosage regimes

Of four persons given 3.5 mg/kg for *S. mansoni* infections only two returned for the four-month examination and neither was cured. At this high dosage level, two of the four persons vomited excessively. An adult female in poor condition (anaemic and malnourished) was given 2 mg/kg. She tolerated the drug well and was cured of a light *S. mansoni* infection. Of three persons given 2.5 mg/kg, one vomited severely. One was cured at the four-month follow-up and egg excretion of the other two was markedly reduced.

Discussion

Present Trials

In the present *S. mansoni* trials, although the cure rate at four months of persons given 3 mg/kg is only 12/38 (31.6%), the overall reduction in egg load in non-cured cases is 87.4%; the reduction in the heavy and very heavily infected groups is 95.8 and 98.2% respectively. This feature of a marked reduction in egg excretion in a therapy regime requiring one single injection gave promise that hycanthone may be a very useful antischistosomal drug, particularly in control schemes.

The cure rate at the four-month follow-up is much lower than at the one and two-month examinations. This could be due to one or more of three factors:

1. Reinfection of some persons after treatment.
2. The possibility that some patients harboured immature schistosomes at the time of treatment and these schistosomes had commenced egg laying at the four-month but not at earlier examinations.

3. Relapse because oviposition of some adult female schistosomes had been temporarily suppressed by treatment.

Of 13 persons negative at two and positive at four months, seven gave histories of not being in contact with bilharzial contaminated water both following and several months prior to treatment. This tends to exclude the first and second possible factors and makes it probable that temporary suppression of oviposition is the main reason for the disparity of cure rates at the earlier and four-month follow-up examination.

In the present trials the four month follow-up results are more reliable for evaluating drug efficacy than the earlier examinations. A WHO scientific group presumed that female schistosomes temporarily sterilised by drugs would have recommenced egg production three months after treatment in the majority of cases (WHO, 1966). Nevertheless, a longer follow-up period (preferably six months) may be required to detect possible late relapses.

Children given hycanthone had a lower cure rate and lower percentage of egg reduction than adults. In the case of children, it is more difficult to exclude factors 1 and 2 mentioned above, as children tend to have more frequent and prolonged contact with contaminated water than adults. But, many factors may be involved. The adolescent group of the present trials, despite a much heavier egg load, had a better response to therapy than the younger group. Many of the adolescents swam regularly in Lake Victoria. Similar lower cure rates in children have been reported in niridazole therapy by several workers (Jordan, 1966; McMahon and Kilala, 1966; Clarke and Blair, 1969; Jarumilinta et al., 1968). There is

a possibility that a more rapid metabolism of both drugs in the case of children, reduces both the level and the duration of the effective drug concentration, or that a different immunological status of the groups may be one cause of the different results.

Nevertheless some persons not cured (children, adolescents and adults) had not been in contact with contaminated water after or several months prior to therapy and these persons can be regarded as failed cures. The failure of one drug to cure could conceivably be due to host factors affecting the absorption, metabolism or excretion of the drug. It is of interest that eight persons, who were not cured of light infections by hycanthone, had also not been cured by optimum dose regimes of other antischistosomal drugs. These had been given during the two years prior to the hycanthone injection. Of these eight, three were adults anxious to be rid of schistosomiasis. They had reasonable standards of living, piped water in their houses and yet remained uncured. One had received stibocaptate (Astiban) and niridazole, the second niridazole and lucanthone and the third had received stibocaptate three months prior to hycanthone therapy. Schistosomes are blood flukes and the failure of three drugs to eliminate them could conceivably be due to some schistosomes being insensitive to the blood concentration attained. Nelson and Saoud (1968) noted that «an interesting recent development in medical biology has been the clear demonstration of infraspecific variations in the biological properties of parasites». Coles (1973) has shown clear-cut biochemical differences in *S. mansoni* obtained from three distinct sources (Entebbe, West Nile and Egypt). As different geographical strains may differ in susceptibility to chemotherapy, it is also conceivable that bioche-

mical differences, within the same geographical strain of *S. mansoni* may result in some of the organisms being less sensitive to therapy than others.

Following further investigations against *S. mansoni* in East Africa with a dosage of 3 mg/kg of hycanthone Ongom (1971) and Rees et al. (1970) considered that still further trials were needed to ascertain an optimum dose. Eyakuze and Rugemalila (1974) compared single intramuscular doses of 3 mg/kg of hycanthone and 30 mg/kg of oxamniquine and noted cure rates of the latter drug to be superior (79% compared to 50%) two months after treatment.

Rees et al. (1974) reported a single injection of 1.5 mg/kg of hycanthone to result in a cure rate of 65% 3 months after treatment. A marked decrease in egg excretion occurred in the non cured persons.

Summary

- 1) A single intramuscular injection of hycanthone in a dosage of 3 mg/kg was given to 63 persons with schistosomiasis. Another 8 persons received other dosage regimes.
- 2) Adults responded better to treatment than children, but reduction in egg excretion was high in all age groups, in both *S. mansoni* and *S. haematobium* infections.
- 3) Vomiting was the main side effect and, in some instances, was excessive and severe.
- 4) The optimum dosage for *S. mansoni* infections in East Africa appears to be 1.5-2.0 mg/kg.

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SUSCEPTIBILITY OF SCHISTOSOMES TO CHEMOTHERAPY WITH PARTICULAR REFERENCE TO HYCANTHONE

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The sensitivity of adult *Schistosoma mansoni* to hycanthone was unchanged after treatment of mice harboring a 15 day old immature infection with a single intramuscular injection of 50 mg (base)/kg of the mesylate salt. Furthermore, no induction of resistance was observed among a population of progeny *S. mansoni* worms whose antecedents as 15 and 30 day old infections were exposed to 50 mg (base)/kg (Yarinsky & Freele, 1974). Previously, Jansma et al. (1974) reported resistance to hycanthone by four of five *S. mansoni* strains whose parent lines as 28 day old infections had been exposed to single doses of 3 or 60 mg/kg. Dr. E. Bueding informed the author (personal communication) that one of the strains made resistant was a Puerto Rican line (SWRI-PR) of the parasite he obtained from our laboratory in January, 1972.

As a consequence of these communications, the experiments reported herein were undertaken with the objectives:

1. To confirm or refute their finding that hycanthone induces resistance among a population of 28 days old schistosomes of the SWRI-PR strain so that the adult worms and/or progeny worms become insensitive to therapy with the drug.

2. To determine whether there is a difference in response to hycanthone by schistosomes derived from intraperitoneal

and percutaneous methods of cercarial infection.

Materials and Methods

The experimental protocol is illustrated in Fig. 1 and is similar for percutaneously (PC) and intraperitoneally (IP) infected mice except where indicated below. In one experiment, each mouse (18-20 g, female Swiss) of two groups (A,B) was injected IP with 200 cercariae of the Sterling Winthrop-Puerto Rican (SWRI-PR) strain of *S. mansoni*. In a second experiment, the animals of groups A and B were placed in restrainers and infected PC by tail immersion to a sufficient number of cercariae to ensure an adequate infection. After 30 min. exposure to the cercariae, the tails were air dried and the animals were caged.

Twenty-eight days after infection, each of the mice harboring prepatent worms in subgroups AA and AB of the PC and IP infected group A was injected intramuscularly into the *vastus lateralis* muscle with a single 50 mg(base)/kg dose of hycanthone mesylate (HM) (Etrenol[®] — Lot No. RO11EC). (Although this dosage of drug has been found to consistently produce high worm mortality, it is nevertheless subcurative against mature infections in mice). The drug was solubilized in distilled water, and the injections were given on a volume to body

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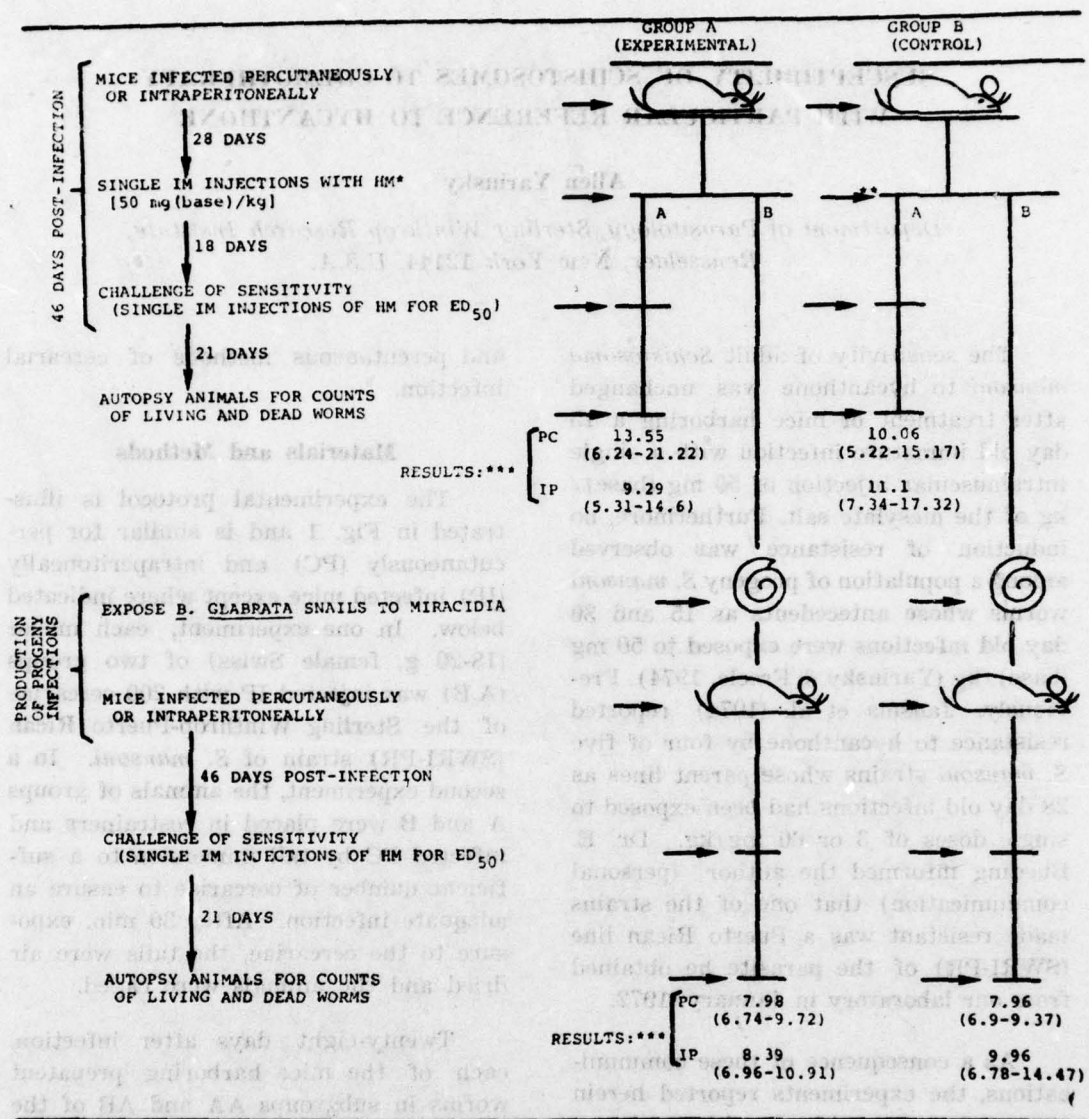


Fig. 1. — Effectiveness of hycanthone mesylate against adult *Schistosoma mansoni* worms and their progeny following an attempt to induce resistance by pretreatment of a 28 day old infection in mice with a single intramuscular dose of 50 mg (base)/kg.

(*) Hm Hycanthone mesylate

(**) Sham treatment

(***) ED₅₀ values (mg/kg with 95% confidence limits) were calculated by the Bliss Weighted Least-Squares Method for Quantal Response Data.

weight basis so that each animal received the required dosage in a volume not exceeding 0.1 ml/50 g body weight. The PC and IP subgroups BA and BB control animals were sham treated with the distilled water vehicle only.

Forty-six days after infection (18 days after exposure of the 28 day old PC and IP subgroups AA and AB worms to 50 mg(base)/kg HM), at which time the schistosomes were sexually mature egg-laying parasites, mice of subgroup AA of the animals infected PC and IP were medicated with single intramuscular injections of HM [3.125 and/or 6.25, 12.5, 25.0, 50.0 mg(base)/kg], prepared and administered as described above. Sham-treated animals were also included in subgroup AA. In addition, control mice of subgroup BA of the PC and IP infected animals not previously exposed to the drug were given intramuscular injections with similar dosages of HM.

Twenty-one days later (67 days post-infection) the animals of subgroups AA and BA were sacrificed and their mesenteric veins and livers were examined for live and dead schistosomes (Yarinsky, 1975). The slopes and ED_{50} 's of the dose response curves (with 95% confidence limits) were calculated by the Bliss Weighted Least-Squares Method for Quantal Response Data (Bliss, 1952).

Following the 67th day post-infection autopsies, miracidia were hatched from eggs derived from schistosomes in surviving animals of subgroups AB and BB of the PC and IP infected mice and were passaged through *Biomphalaria glabrata* snails. The F_1 progeny worm generations were re-established in mice following the PC and IP infection procedures respectively as for their antecedents. (Note: Only a few mice could be infected IP to establish the experimental subgroup AB and control subgroup BB F_1 generations

inasmuch as a small number of cercariae were harvested from snails. These infections were, therefore, cycled again through snails, which yielded sufficient cercariae to IP infect a larger number of animals with the AB and BB F_2 generations of schistosomes).

Mice harboring the F_1 (PC) and F_1 (IP) 46 day old infections (subgroups AB and BB) were medicated with single intramuscular doses of HM [3.125, 6.25, 12.5, 25.0, 50.0 mg(base)/kg]. Both IP and PC subgroups AB and BB also included nonmedicated, sham treated mice. Twenty-one days later the animals were sacrificed and necropsied, live and dead worms were counted, and the data statistically analyzed as before.

Results

1. *Activity of HM against 46 day old (adult) S. mansoni earlier exposed as 28 day old prepatent worms to 50 mg(base)/kg of the drug (Table 1).*

Intraperitoneally infected mice. The data in the upper portion of Table 1 clearly show that adult worms of an HM pretreated 28 day old schistosome infection responded to therapy no differently than adult worms of the control infection that did not receive exposure to the drug as 28 day old worms. The ED_{50} 's (9.29 and 11.1 mg/kg) achieved by the drug against the schistosomes in both groups of animals were not significantly different ($P > 0.05$). It should also be noted that the slopes of the two dose response curves (2.4 ± 0.6 and 3.0 ± 0.7 , respectively) were not significantly different.

Percutaneously infected mice. As for IP infected mice, the data in the lower portion of Table 1 show no difference in the response by adult worms that were pretreated with HM as 28 day old prepatent schistosomes and a comparable

TABLE 1. Activity of hycanthone mesylate in mice against 46 day old (adult) *Schistosoma mansoni* (SWRI-Puerto Rican strain) previously exposed as 28 day old prepatent worms to 50 mg(base)/kg of the drug.

Method of infection	Hycanthone-mg(base)/kg, IM		Number of mice	Average No. worms found				Worms Dead	ED ₅₀ mg/kg* (95% Confidence limits)
	At 28 days Post-Inf.	At 46 days Post-Inf.		Liver		Mesenteric veins			
				Live	Dead	Live	Dead		
EXPERIMENT I									
Intraperitoneal	50	50	10	0	9.5	0.4	0	96.0	9.29 (5.31-14.6) [Slope=2.4±0.6]
	50	25	9	0.1	7.8	0.7	0	91.0	
	50	12.5	9	1.4	4.1	1.8	0	56.0	
	50	6.25	9	2.3	2.7	4.2	0	28.9	
	50	3.125	10	2.0	1.4	4.9	0	16.9	
	50	0**	10	2.0	0.8	5.0	0	10.1	
	0**	50	10	0	8.7	0.3	0	96.9	
	0**	25	9	0.2	4.9	0.4	0	88.0	
	0**	12.5	10	0.5	4.5	2.6	0	59.4	
	0**	6.25	9	1.1	2.2	7.8	0	20.0	
0**	3.125	10	1.9	0.5	6.3	0	5.8	11.1 (7.34-17.32) [Slope=3.0±0.7]	
0**	0**	9	2.1	0	7.4	0	0		
EXPERIMENT II									
Percutaneous	50	50	7	0	7.7	0	0	100	13.55 (6.24-21.22) [Slope=3.5±1.1]
	50	25	7	0	6.3	1.9	0	77.2	
	50	12.5	6	0.7	1.7	1.0	0	50.0	
	50	6.25	7	1.1	0.7	3.6	0	13.2	
	50	0**	4	1.2	0	4.3	0	0	
	0**	50	10	0	7.4	0	0	100	
	0**	25	9	0	6.7	0.7	0	91.0	
	0**	12.5	10	0	3.6	1.8	0	66.5	
	0**	6.25	9	0.4	1.7	5.6	0	21.8	
	0**	0**	8	2.6	0	7.1	0	0	

(*) The ED₅₀ values and slopes for the dose response curves were calculated by the bliss weighted least-squares method for quantal response data.

(**) Sham treatment.

control group of adult worms that had been exposed to a distilled water sham treatment when they were 28 days old. The ED_{50} 's against the schistosomes in both groups of animals (13.55 and 10.06 mg/kg) were not significantly different. In addition, the slopes of the two dose response curves (3.5 ± 1.1 and 3.6 ± 1.1) were equivalent.

2. *Activity of HM against 46 day old (adult) S. mansoni progeny schistosomes whose antecedents as 28 day old worms were exposed to 50 mg (base)/kg of the drug (Table 2).*

Intraperitoneally infected mice. Adult schistosomes of the F_2 generation, whose antecedents as 28 day old worms were exposed to HM [50 mg(base)/kg] were as sensitive to therapy ($ED_{50} = 8.39$ mg/kg) as the F_2 schistosomes of the control infection ($ED_{50} = 9.96$ mg/kg) whose antecedents received sham treatment. The slopes of their dose response curves (3.0 ± 0.6 and 2.9 ± 0.6 , respectively) were similar, thus establishing the equipotency of HM against the two adult progeny worm infections.

Percutaneously infected mice. The susceptibility of the F_1 progeny adult worms to therapy with HM was unaltered following the attempt to induce resistance by exposure of antecedent 28 day old worms to 50 mg(base)/kg of the drug. The ED_{50} of 7.98 mg/kg for HM against this infection was no different than the ED_{50} of 7.96 mg/kg achieved by the drug against the F_1 worms of the control sham treated mice. Moreover, the slopes of the two dose response curves (3.3 ± 0.6 and 3.2 ± 0.5 , respectively) were equivalent.

Discussion

At the conditions under which these experiments were conducted, induction and subsequent genetic transmission of

resistance to hycanthone did not occur; adult progeny of worms obtained after treatment of mice harboring prepatent 28 day old schistosomes with 50 mg (base)/kg were as susceptible to therapy with HM as were adult schistosomes whose antecedents had not been exposed to the drug. It is also evident from the equivalent dose response data derived from the two experiments that the method of infection (PC or IP) did not affect the response by adult worms to therapy with HM.

In studies with another schistosomicide, tris (*p*-aminophenyl) carbonium pamoate, Thompson et al. (1965) was unable to induce resistance to a Puerto Rican strain of *S. mansoni*. Following therapy with a subcurative course of the drug (0.125% in the diet from 23 through 37 days after infection) to each of three consecutively cycled prepatent infections, no evidence of drug resistance was obtained; adult egg-laying progeny schistosomes were as susceptible to the drug as were worms of the parent line.

A number of studies with experimentally infected animals have revealed intrinsic strain specific differences in the susceptibility of schistosomes to chemotherapeutic agents. Gönner and Vogel (1955) found in Krispien mice that a Liberian strain of *S. mansoni* was more sensitive to lucanthone than was an Egyptian strain. Thompson et al. (1965) also reported a murine infection with a Liberian strain of *S. mansoni* to be more sensitive than a Puerto Rican strain of the parasite to chemotherapy with tris (*p*-aminophenyl) carbonium pamoate. Furthermore, Thompson et al. (1962) attributed the poor sensitivity of their strain of *S. mansoni* to lucanthone to variability in drug susceptibility among strains of the parasite. It was not remarkable, therefore, that in the same laboratory the

TABLE 2. Activity of hycanthone mesylate in mice against 46 day old adult progeny *Schistosoma mansoni* (SWR1-Puerto Rican strain) whose antecedents as 28 day old prepatent worms were exposed to 50 mg (base)/kg of the drug.

Method of infection	Hycanthone-mg(base)/kg, IM		Average No. Worms Found				ED ₅₀ mg/kg* (95% confidence limits)	
	at 28 days Post-Inf.	at 46 days Post-Inf.	Number of Mice	Mesenteric veins		% Worms dead		
				Liver	Mesenteric veins			
	to antecedents	to progeny		Live	Dead	Live	Dead	
EXPERIMENT I								
Intraperitoneal	50	50	8	0	10.6	0.5	0	95.5
	50	25	10	0	8.3	1.4	0	85.5
	50	12.5	10	0.2	7.1	2.4	0	73.2
	50	6.25	9	0.4	2.8	7.0	0	27.2
	50	3.125	10	1.6	0.6	11.2	0	4.5
	50	0**	6	0.8	0	9.3	0	0
	0**	50	10	0	13.3	0	0	100
	0**	25	10	0	7.6	0.9	0	89.5
	0**	12.5	6	0.4	7.0	2.6	0	70.0
	0**	6.25	8	0.6	4.0	6.6	0	35.6
0**	3.125	8	1.3	0.6	10.4	0	5.1	
0**	0**	9	0.8	0	10.1	0	0	
EXPERIMENT II								
Percutaneous	50	50	9	0	27.5	0.4	0	98.5
	50	25	10	0	21.8	0.8	0	96.5
	50	12.5	10	0	10.1	4.9	0	67.4
	50	6.25	10	0.4	6.3	9.7	0	38.5
	50	3.125	10	2.2	1.1	17.9	0	5.2
	50	0**	10	3.5	0	16.1	0	0
	0**	50	10	0	17.3	0.2	0	98.9
	0**	25	10	0.6	16.0	0.8	0	94.6
	0**	12.5	10	0.2	9.8	3.8	0	71.0
	0**	6.25	10	0.7	4.0	5.7	0	38.5
0**	3.125	10	1.4	0.7	16.4	0	3.8	
0**	0**	9	3.9	0	12.2	0	0	

(*) The ED₅₀ values and slopes for the dose response curves were calculated by the Bliss weighted least-squares method for quantal response data.

(**) Sham treatment.

structurally closely related compound, hycanthone, also exhibited poor antischistosomal activity in mice and hamsters (Elslager, 1970).

Taylor and Nelson (1971) provided evidence that a Tanzanian strain of *S. mansoni* in mice was more resistant to niridazole than a strain of the parasite of Puerto Rican origin. Lee et al. (1971) showed that male schistosomes of an NIH-PR strain of *S. mansoni* which had been passaged in their laboratory for many years were more sensitive to hycanthone than male worms of more recently isolated Belo Horizonte, Liberian, and St. Lucian strains. Interestingly, their data suggest the NIH-PR strain to be less sensitive to stibophen than the W-PR strain also from Puerto Rico as well as strains of *S. mansoni* from Liberia, St. Lucia, and Belo Horizonte. The authors also noted that the male worm of «the NIH-PR and Liberia strains appeared to be slightly more susceptible than that of St. Lucia and Belo Horizonte strains» to lucanthone. Although Lee et al. (1971) found male worms of a Liberian and a Puerto Rican strain to be similarly susceptible to lucanthone, Bruckner (1974) observed that both unisexual and bisexual infections with a Puerto Rican strain to be less sensitive to this drug than the Liberian strain. Evidently the Puerto Rican strains used by both workers were derived from different sources. Foster and his co-workers (1971, 1973) reported UK 3883 as well as its fermentatively derived 6-hydroxymethyl analog, UK 4271 (oxamniquine), to have greater efficacy against a Puerto Rican strain of *S. mansoni* than against an East African strain of the same parasite.

Bueding et al. (1973) noted differences in murine infections in response to hycanthone and a chloroindazole analog (IA-4) among strains of *S. mansoni* from Liberia, Tanzania, and St. Lucia. Differences

in susceptibility to the two schistosomicides were also observed among strains of similar geographic origin; single intramuscular doses of 16 and 32 mg/kg of IA-4 or hycanthone produced none to minimal (4%) parasitologic cures in mice infected with the Puerto Rican M strain, whereas at the same dosages 34%-67% of the mice infected with the Puerto Rican SW and WR strains were parasitologically cured.

Experiments at the Sterling Winthrop Research Institute (SWRI) have shown that hycanthone was as efficacious in mice and hamsters against two different strains of *S. mansoni* of St. Lucian origin as against a Puerto Rican strain of the schistosome maintained at the Institute for more than 25 years. In contrast, the drug was significantly less active in both rodents against the Puerto Rican M strain of the parasite (Farah et al., 1974).

Differences in susceptibility of schistosomes to experimental chemotherapy is not restricted to *S. mansoni*. For example, it was shown by Hsü et al. (1963) that the Japanese strain of *S. japonicum* in mice was less sensitive to treatment with the antimonials, tartar emetic and stibophen, than were Chinese, Formosan and Philippine strains of the parasite.

Although reports from different laboratories of the effectiveness of chemotherapeutics cannot easily be compared due to difference in techniques and criteria for efficacy, it is evident from the preceding that comparative studies within laboratories have confirmed that strains of schistosomes of the same species, whether of different or similar geographic origins, may differ in response to chemotherapy with the same agent.

Rogers and Bueding (1971) reported that six to twelve months after single intramuscular injections of 30 and 60 mg/kg hycanthone to mice infected with a

Puerto Rican M strain of *S. mansoni*, surviving schistosomes that were initially caused to shift from the mesenteric veins to the liver and were observed to be functionally and morphologically abnormal, recovered and returned to the mesenteric veins. The female worms produced eggs which gave rise to a population of adult schistosomes found to be resistant to an 80 mg/kg intramuscular dose of the drug. They also reported that the same strain of the parasite was made resistant to hycanthone in hamsters. The same laboratory observed cross resistance by the schistosome to the structurally related antischistosomal, lucanthone, oxamniquine and two chloroindazoles (IA-3 and its hydroxymethyl derivative, IA-4) (Rogers & Bueding, 1971; Bueding et al., 1973). Experiments at SWRI confirmed the decreased susceptibility to hycanthone of an F₁ generation of the Puerto Rican M strain of schistosome whose antecedents (as adults) in murine infections were treated with a single intramuscular dose of 60 mg/kg, while a 30 mg/kg dose had not induced resistance [unpublished data].

Attempts to induce resistance to hycanthone by the treatment of sexually mature parasites of another Puerto Rican strain (SWRI-PR) of *S. mansoni* in mice (Yarinsky et al., 1974) and hamsters (unpublished data) as well as of *S. haematobium* (Fripp, 1974) have not been successful. Foster and Cheetham (1973) were also unable to confirm drug resistance, in this case to oxamniquine, with yet another strain of *S. mansoni* of Puerto Rican origin. In this connection, they stated, «Puerto Rican worms derived from the survivors of treatment of a previous generation with a subcurative dose of oxamniquine were as susceptible to the drug as their parents». Cline (personal communication) did not succeed in inducing resistance among schistosomes ob-

tained from a freshly isolated infection from untreated patients in Puerto Rico and established in mice intramuscularly injected with 12.5 and 60 mg/kg HM.

Efforts have been made to demonstrate the phenomenon of drug resistance with material derived from incompletely cured patients. Webbe and James (in press) obtained St. Lucian strains of *S. mansoni* from patients who were treated but not completely cured with hycanthone and lucanthone as well as from an untreated case. The infections, which were passaged in mice, responded to therapy with a single intramuscular injection of 80 mg/kg hycanthone, and four oral doses of 200 mg/kg lucanthone, respectively; viable ova were not obtained from any of the mice treated with either of the drugs. Moreover, murine infections established from eggs isolated from the untreated patient and the lucanthone treated patient also responded to therapy with hycanthone. Relevant to this is the work reported by Cook et al. (1974). They followed 143 patients in St. Lucia for two years after treatment with hycanthone and found no evidence to suggest the emergence of resistance. The failure of resistance to hycanthone to appear among progeny of *S. haematobium* derived from uncured cases was observed by Fripp (1974). He collected eggs from pooled urine samples of children who had not been completely cured after therapy with hycanthone and passaged the hatched miracidia through *Bulinus africanus* snails. Emergent cercariae were used to infect the rodent, *Saccostomus campestris*. These animals, as well as a group infected with *S. haematobium* that had never been exposed to therapy, were injected with a dose of hycanthone calculated to produce an LD₅₀ for the worms. Approximately five weeks after therapy, eggs were collected, hatched, and fresh infections established in snails, and thence

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PROCEEDINGS OF THE INTERNATIONAL CONFERENCE ON SCHISTOSOMIASIS --ETC(U)

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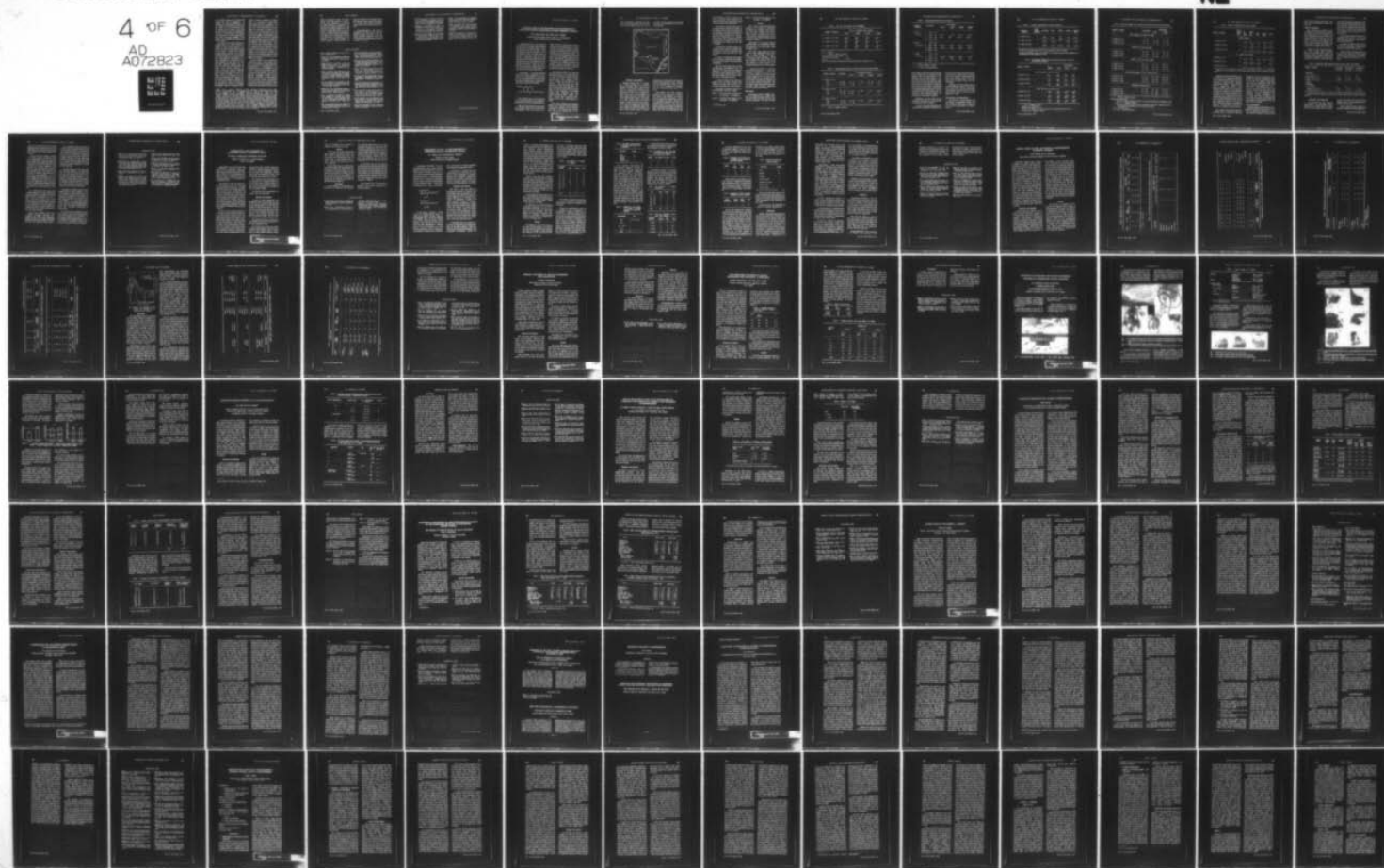
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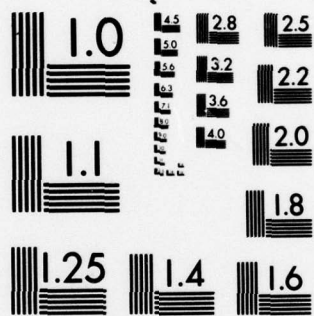
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to the rodents which were treated with another LD₅₀ dose of hycanthone. At autopsy, «no significant difference was seen between the percentage reduction in the number of live flukes obtained from the treated rodents infected with either the wild (human) strain or the laboratory strain of *S. haematobium*». This finding was confirmed in a second experiment in which five consecutive passages of the infection were completed in subcuratively treated rodents.

In contrast to the aforementioned experiences, Katz et al. (1973) reported resistance in mice among progeny of *S. mansoni* derived from eggs from the feces of two patients in Brazil after therapy with hycanthone consisting of two intramuscular injections at 2.5 mg/kg spaced three months apart and a course of treatment with niridazole (25 mg/kg/d × 5 days). Although the combination of therapies reduced the egg output by more than 95%, sufficient numbers were obtained to infect snails with miracidia. As judged by the oogram technique, the murine schistosome infection exhibited resistance to both hycanthone and niridazole. Cross resistance of this strain (dubbed WW) to oxamniquine also occurred. In discussing their results, Katz et al. (1973) were unable to conclude whether the resistant strain of schistosome was obtained by selection or induction. Interestingly, Foster & Cheetham (1973)

could not confirm resistance to another strain of *S. mansoni* of Puerto Rican origin after subcurative treatment of a murine infection with oxamniquine. Another case of unresponsiveness to hycanthone was uncovered by Campos et al. (1975) in mice infected with *S. mansoni* derived from eggs recovered from a patient whose infection persisted after three treatments with the drug. He concluded that «the resistance was not intrinsic to the parasite». Presumably he meant that the resistance was drug induced. However, the fact that he also isolated eggs of *S. mansoni* from an untreated patient in the same area which gave rise to schistosomes in mice that were sensitive to therapy with hycanthone strongly suggests that more than one strain of schistosome was present with differing susceptibility to treatment.

Clearly, further work is required in defining the nature of schistosome resistance to thioxanthenes, aminomethyltetrahydroquinolines, chloroindazoles and nitrothiazoles, and cross resistance by the worms to related and unrelated members of these chemical classes. The observations that *S. mansoni* from the same and different geographic locations exhibit different sensitivities to chemotherapy should encourage further investigations with special emphasis on obtaining fresh material from the field. Finally, in view of substantial experimental evidence* that

* Included among numerous references describing intraspecific differences between schistosomes are: Anderson, L.A. and Cheever, A.W. 1972. Bull. WHO, 46:233-242; Bruckner, D.A. and Schiller, E.L. 1974. J. Parasitol., 60:551-552; Cridland, C.C. 1970. Bull. Wild Hlth Org., 43:809-815; James, C. and Webbe, G. 1973. J. Helminth., 47:49-59; Magalhaes, L.A. and Carvalho, J.F. 1973. Revta Saude Publ., 7:289-294; Magzoub, M. and Adam, S.E.I. 1974. Br. J. exp. Path., 55:260-268; Paraense, W.L. and Correa, L.R. 1973. Rev. Inst. Med. trop. Sao Paulo, 15:127-130; Powers, K.G. and Cheever, A.W. 1972. Bull. Wild Hlth Org., 46:295-300; Richards, C.S. 1975. Parasitology, 70:231-241; Ruff, M.D., Davis, G.M. and Werner, J.K. 1973. Exp. Parasitol., 33:437-446; Sadun, E.H., von Lichtenberg, F. and Bruce, J.J. 1966. Am. J. trop. Med. Hyg., 15:705-718; Saeed, A.A. and Hussein, M.F. 1974. J. Helminth., 48:205-212; Taylor, M.G. 1970. J. Helminth., 44:253-314; Taylor, M.G. and Andrews, B.J. 1973. J. Helminth., 47:439-453; Taylor, M.G., Nelson, G.S., Smith, M. and Andrews, B.J. 1973. J. Helminth., 47:455-485; Warren, K.S. and Berry, E.G. 1972. J. infect. Dis., 126:482-491; Webbe, G. and James, C. 1971. J. Helminth., 45:271-284; Webbe, G. and James C. 1971. J. Helminth., 45:403-413; Wright, C.A. and Knowles, R.J. 1972. Trans. roy. Soc. trop. Med. Hyg., 66:108-118; Wright, C.A. Southgate, V.R. Van Wijk, H.B. and Moore, P.J. 1974. Trans. roy. Soc. trop. Med. Hyg., 68:413-414.

different geographic strains of schistosomes of the same species, as well as hybrids, show differences in infectivity for snails, differences in infectivity for experimental animals, differences in egg and adult morphology, differences in prepatency periods, differences in egg production, and differences in pathogenicity, it should also be determined whether these differences are significant in contributing to any observed instance of altered response to chemotherapy. Be-

cause of variations in biological behavior that appear to exist among schistosomes, it is urged that careful comparative studies be made of their genetic constitution.

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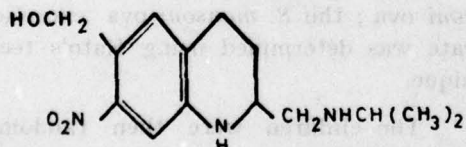
A CLINICAL TRIAL OF THE TREATMENT WITH OXAMNIQUINE OF *SCHISTOSOMA MANSONI* INFESTATION IN SCHOOL CHILDREN IN KENYA

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Schistosomiasis is a well recognised major clinical and public health problem in many parts of Africa, South and Central America and the Far East. Many authorities consider the problem to be on the increase. So far, no single method of control or eradication has been found effective. Sanitation combined with the destruction of the snail vector and chemotherapy remain the best approach to control and eradication. There are still no effective drugs safe for mass administration under minimal medical supervision, and the search for such drugs goes on.

Oxamniquine, a recently developed drug of the Pfizer Laboratories for the treatment of schistosomiasis, is a derivative of tetrahydroquinoline evolved from the Bayer mirasans group of schistosomicides whose formula is as follows :



The chemical name of the compound is d-1,6-hydroxymethyl-2-isopropylamino-methyl-7-nitro-1,2,3,4-tetrahydroquinoline.

Oral and intramuscular preparations are available. Single dose intramuscular administration has been shown to be

highly effective in the treatment of *Schistosoma mansoni* infestations in a number of trials, e.g. Silva et al. (1974) in South America and Eyakuze (1974) in Mwanza, Tanzania, with a cure rate of 89% ; but in *S. haematobium* infestation it has been found to be only slightly effective. However, intramuscular administration produces severe and crippling pain at the site of injection and, although it produces no toxicity or serious side effects, it cannot be recommended for routine or mass administration because of this pain.

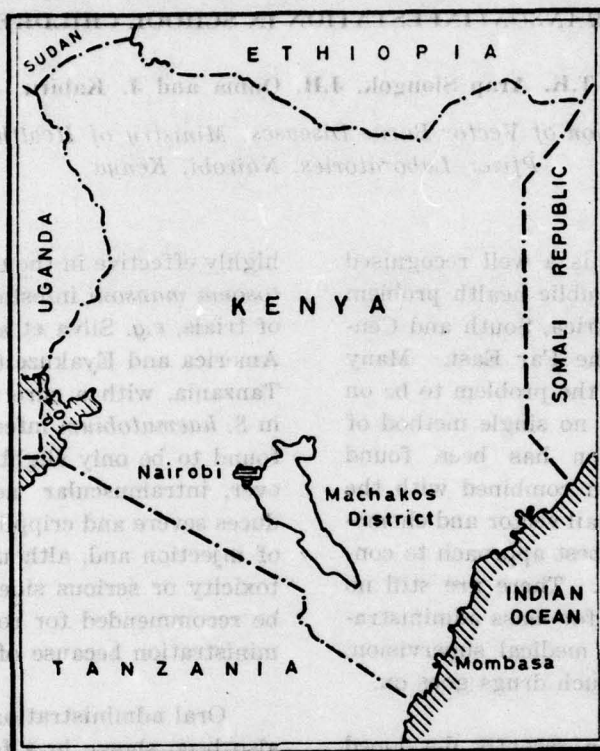
Oral administration for 1-2 days has also been shown in a few trials in South America and Africa to be highly effective, e.g., Silva et al. (1974) in South America obtained 81.5% cure, Eyakuze in Tanzania a 67-80% cure and over 90% egg reduction. The same trials and other similar ones have shown the drug to be safe with minimum side effects. It compares well and is even better than other drugs in the treatment of *S. mansoni* (Jordan, 1965 ; McMahon, 1967 ; McMahon & Samatta, 1969 ; Clarke et al., 1969 ; Ongom, 1971 ; Eyakuze, 1974 ; Roberts & Rees, 1974 ; McCullough et al., 1974).

This paper describes and discusses results of a clinical trial being conducted among school children with *S. mansoni* infestation in the Machakos area in Kenya some 100 km from Nairobi (Fig. 1). The

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study is designed to determine the efficacy of oral oxamniquine and the optimum effective dosage regime as well as

its safety and side effects with particular reference to its suitability for use in mass chemotherapy.



Materials and Methods

Machakos district (Fig. 1) in Kenya has a high prevalence of *S. mansoni*. Mutinga & Ngoka (1971) found school children in his district to have a prevalence rate ranging from 21.3-42.2% distributed all over the area. A recent population survey done by the Division of Vector Borne Diseases in the Nduu area of the same district shows a prevalence rate of 80%. Twelve months ago several primary schools in the area were screened for ova in the stools and particularly for *S. mansoni* infestations using Ritchie's method. Two of the schools in the survey which showed a high *S. mansoni*

infestation rate were chosen for this trial. Further stool specimens were collected from the children found to have *S. mansoni* ova; the *S. mansoni* ova excretion rate was determined using Kato's technique.

The children were then randomly allocated in three groups for treatment. The medical team involved (two doctors and four laboratory technicians) carried out a physical and clinical examination on each child included in the trial and collected samples of urine and blood for analysis. These samples were transported back to Nairobi for analysis on the following day. The team administered the

drug themselves, at 6-8 hr between the doses, on each day. They remained at the school until the school was closed to deal with any problem that might arise.

On the 3rd or 4th day after the 1st day of treatment as many as possible of the children in the trial were questioned for side effects and further specimens of urine and blood samples were collected. Stools were examined for the *S. mansoni* ova excretion rate on approximately the 10th day after treatment, and then approximately every month from the day of treatment.

It is planned to continue monthly examination of the stools for a period of 12 months from the day of treatment. So far the follow-up has been done for nine months.

On about the 3rd month after treatment, as many as possible of the children in the trial had another clinical physical examination.

The two schools which were selected had 200 pupils, all Kamba by tribe. Of these 127 were found to have *S. mansoni* infestation — a prevalence rate of 63.5%. The group tested included 123 of them. Their ages ranged from 9-17 years except for one who was aged 24 years.

At various stages of the follow-up, children were lost either because they refused to continue with the trial or because they transferred to other schools.

The groups of children received various treatment regimes as follows:

Group 1: 15 mg/kg body weight b.d.* for one day — 60 children.

Group 2: 10 mg/kg body weight b.d. for two days — 32 children.

Group 3: 15 mg/kg body weight b.d. for two days — 31 children.

Results

Cure rates in the three treatment regimens at 1-3 months, as determined by absence of *S. mansoni* ova excretion, were very high, ranging from 94.4%-100% in all the 3 groups at one month to 89.7%-96.5% at three months, with an overall cure rate of 93.3% at three months as shown in Table 1.

Comparison of the three treatment regimens shows no statistically significant difference in the cure rates using Friedman's test.

The mean egg counts at various stages of stool examination after treatment, i.e., after 10 days, 1, 2 and 3 months, show great reduction (Tables 2, 3) ranging from about 90-95% at 10 days, to 100% at 1-3 months. The overall egg reduction at three months in all treatment regimens was practically 100%.

A total of 63 children in this trial had a stool examination nine months after treatment. Of these 30 were in the 15 mg/kg body weight b.d. for the one day treatment regimen, 21 were in the 10 mg/kg body weight b.d. for two days and 12 were in the 15 mg/kg body weight b.d. for two days regimen of treatment. The cure rates at nine months after treatment were 90%, 100% and 95% respectively and the overall rate was 93.7%.

Side effects

Drowsiness, nausea, vomiting, headache and abdominal pain usually occurring 1-6 hr after treatment were the most frequent symptoms. But none of them

* bis d'e (twice a day).

TABLE 1. Cure rate after treatment with Oxamniquine.

Regimen of treatment	Time of examination after treatment			
	10 days	1 month	2 months	3 months
15 mg/kg b.b./1 day*	75.8% (33)**	100% (38)	94.4% (39)	89.7% (39)
10 mg/kg b.d./2 days	20.9% (24)	100% (29)	100% (27)	96.2% (26)
15 mg/kg b.d./2 days	50% (28)	100% (23)	100% (22)	96.5% (24)

*b.d. twice daily

** () Number of children examined

Total followed up for three months = 89

Total cured at three months = 83

% cure = 93.3%

The three cure rates after three months show no significant difference (Friedman's test).

TABLE 2. Mean and range of egg count per gram of faeces before and after treatment

Regimen of treatment	Pretreatment	Post-treatment egg output			
		10 days	1 months	2 months	3 months
15 mg/kg b.d./1 day					
mean	671 (60)*	65 (33)	0 (38)	0.8 (39)	2.3 (39)
range	20 - 2320	0 - 440	0	0 - 20	0 - 40
10 mg/kg b.d./2 days					
mean	981 (32)	45.4 (24)	0 (29)	0 (27)	0.9 (26)
range	50 - 3060	10 - 210	0	0	0 - 10
15 mg/kg b.d./2 days					
mean	937 (31)	41.4 (28)	0 (23)	0 (22)	0.5 (24)
range	10 - 5340	0 - 420	0	0	0 - 20

* () Number of children examined

TABLE 3 Mean egg load reduction per gram of faeces.

Regimen of treatment		Pre-treatment	Post-treatment			
			10 days *	1 month **	2 months ***	3 months ****
15 mg/kg b.d./1 day	*	724.5 (31)				
	**	694.2 (36)	70 (31)	0 (36)	1.0 (39)	2.6 (39)
	***	669.2 (39)	90.3%	100%	99.9%	99.6%
	****	636.9 (39)				
10 mg/kg b.d./2 days	*	1073.6 (25)				
	**	966.9 (29)	46.8 (25)	0 (29)	0 (27)	0.4 (26)
	***	1005.2 (27)	95.6%	100%	100%	100%
	****	1029.6 (26)				
15 mg/kg b.d./2 days	*	835.4 (28)				
	**	1026.2 (23)	43.2 (28)	0.4 (23)	0 (20)	0.4 (25)
	***	682.5 (20)	94.8%	100%	100%	100%
	****	1028.4 (25)				

() Number of children examined.

*, **, etc. indicate corresponding figures.

were severe, as they did not prevent any of the children from continuing to attend school on the day of treatment or on the following day. One child fainted — became very drowsy, was unable to stand and had a very weak and slow pulse about one hr after the first dose of treatment. The child recovered quickly on being laid down flat and given some orange juice. One child developed high fever on the following day and on examination, was suspected to have developed malaria; he recovered on chloroquine treatment.

Drowsiness was the most common complaint and appeared to increase with the dosage as shown in Table 4.

As can be seen from Tables 4 and 7, more children complained of headache on

the day of treatment than before treatment and three months after treatment, whereas the complaint of abdominal pain was more frequent before and three months after treatment than on the day of therapy.

Although these side effects are not serious, statistical analysis (Friedman's test) shows that the 15 mg/kg body weight regimen of treatment for two days (the highest) tended to cause more side effects ($P = 0.02$).

Haematology and biochemistry

The results of haematological and biochemical investigations before and after treatment (three days, 10 days and one month) are presented in Tables 5 and 6.

TABLE 4. Analysis of side effects on the day of treatment

Regimen of treatment	No. of children interviewed	Drowsiness	Nausea	Vomiting	Headache	Abdominal pain
15 mg/kg b.d./1 day	51	36 (70.6%)	8 (15.7%)	2 (3.9%)	7 (13.7%)	12 (23.5%)
10 mg/kg b.d./2 days	31	19 (61.8%)	8 (25.8%)	NIL	10 (32.2%)	9 (29.0%)
15 mg/kg b.d./2 days*	31	25 (80.6%)	3 (9.7%)	5 (16.1%)	13 (41.9%)	4 (12.9%)

*One child of the 3rd group fainted about 1hr after receiving the 1st dose of treatment.

As shown by Friedman's test the two days regimen of 15 mg/kg b.d./two days caused significantly more side effects than the other regimens ($P = 0.02$).

TABLE 5. Haematological findings before treatment and three days, 10 days and one month after treatment.

Regimen of treatment	Pre-treatment	Post-treatment		
		3 days	10 days	1 month
Mean haemoglobin in grams per 100 ml*				
15 mg/kg b.d./1 day	13.3 (45)	13.9 (44)	13.4 (32)	13.1 (39)
10 mg/kg b.d./2 days	13.4 (32)	14.0 (29)	14.1 (14)	13.5 (25)
15 mg/kg b.d./2 days	13.2 (31)	14.2 (28)	13.8 (29)	13.5 (22)
Mean total white cell count per ml**				
15 mg/kg b.d./1 day	7,484 (32)	8,621 (28)	11,128 (14)	8,868 (25)
10 mg/kg b.d./2 days	7,691 (45)	8,293 (44)	10,689 (32)	8,715 (40)
15 mg/kg b.d./2 days	8,838 (31)	9,835 (28)	19,537 (29)	8,086 (22)

() No. of children examined.

Friedman's test showed that :

(*) there was a significant increase of haemoglobin 3 days after treatment ($P=0.01$)

(**) there was no significant difference.

TABLE 6. Biochemical findings before treatment, and ten days and one month after treatment.

Regimen of treatment	Pre-treatment	Post-treatment	
		10 days	1 month
Mean bilirubin* in mg/100 ml serum			
15 mg/kg b.d./1 day	1.3 (17)	1.6 (31)	1.6 (37)
10 mg/kg b.d./2 days	1.16 (14)	1.49 (14)	1.44 (25)
15 mg/kg b.d./2 days	1.3 (17)	1.4 (28)	1.6 (18)
SGOT** in IU. per 100 ml serum			
15 mg/kg b.d./1 day	17.0 (17)	27.6 (31)	27.1 (36)
10 mg/kg b.d./2 days	21.0 (14)	24.3 (14)	25.3 (23)
15 mg/kg b.d./2 days	19.9 (16)	28.0 (28)	23.4 (18)
SGPT** in I.U. per 100 ml serum			
15 mg/kg b.d./1 day	18.9 (17)	27.51 (31)	20.64 (37)
10 mg/kg b.d./2 days	19.9 (14)	32.5 (14)	18.7 (23)
15 mg/kg b.d./2 days	15.3 (16)	24.4 (28)	15.3 (18)
Mean alkaline phosphate*** in K.A. units per 100 ml			
15 mg/kg b.d./1 day	26.3 (17)	29.8 (31)	23.0 (36)
10 mg/kg b.d./2 days	22.9 (14)	25.3 (14)	19.5 (25)
15 mg/kg b.d./2 days	21.0 (17)	20.2 (27)	17.0 (18)
Blood urea** in mg per 100 ml			
15 mg/kg b.d./1 day	16.7 (17)	16.1 (32)	16.5 (37)
10 mg/kg b.d./2 days	19.5 (13)	18.5 (14)	17.3 (25)
15 mg/kg b.d./2 days	17 (17)	18.1 (29)	17.3 (18)

() Number of children examined

Friedman's test showed that:

* there was a significant increase of bilirubin 10 days and one month after treatment ($P=0.05$).

** there was no significant difference.

*** there was a significant increase of alkaline phosphatase 10 days after treatment ($P=0.05$).

This returned to pre-treatment level one month after treatment.

I.U. = international units.

K.A. units = King-Armstrong units.

TABLE 7. Analysis of complaints before and after treatment.

Regimen of treatment	No. of children interviewed	No complaints	Abdominal pain	Headache	Bloody stools	Other
A. Before treatment						
15 mg/kg b.d./1 day	51	14 (29.5%)	31 (60.8%)	3 (5.9%)	13 (25.5%)	5 (9.8%)
10 mg/kg b.d./2 days	32	4 (12.5%)	20 (62.5%)	1 (3.2%)	10 (31.3%)	8 (25.0%)
15 mg/kg b.d./2 days	31	3 (9.7%)	25 (80.6%)	1 (9.2%)	15 (48.4%)	3 (9.7%)
B. 3 months after treatment						
15 mg/kg b.d./1 day	24	17 (70.8%)	21 (87.5%)	3 (12.5%)	2 (8.3%)	4 (16.7%)
10 mg/kg b.d./2 days	25	12 (48.0%)	11 (44.0%)	3 (12.0%)	0	3 (12.0%)
15 mg/kg b.d./2 days	26	15 (57.7%)	5 (19.2%)	4 (15.4%)	0	3 (11.5%)

These data cannot be subjected to critical statistical analysis because they do not refer to the same patients.

Statistical analysis (Friedman's test) of results shows no significant difference in the figures obtained before and after treatment in serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), white blood cell (WBC) and blood urea levels, although there appears to be a slight increase, after treatment, in SGOT, SGPT and WBC levels. These increases are more noticeable in the results obtained three and ten days after treatment and tend to return to pre-treatment levels one month after treatment except in the case of SGOT which does not show this tendency. However, the increases in SGPT and SGOT do not exceed the normal levels.

The results obtained before and after treatment show a statistical difference

(Friedman's test) for haemoglobin (Hb), bilirubin and alkaline phosphatase (Table 6). The Hb and alkaline phosphatase values increase significantly three days after treatment (Friedman's test: $P = 0.01$ and $P = 0.05$ respectively), but return to pre-treatment values when examined at ten days and one month after treatment. The serum bilirubin shows significant increase (Friedman's test $P = 0.05$) three days, ten days and one month after treatment, i.e., the values had not returned to pre-treatment levels one month after treatment.

Urine examinations

Specific gravity measurements, microscopical examinations and tests for protein and sugar were carried out on the urine before treatment, as well as three

days, ten days and one month after treatment, and no significant changes were observed.

Clinical examinations

The most common complaints before treatment were abdominal pain, headache and bloody stools. A few children had other complaints such as pain in the chest, coughing, swelling of the legs and fits. These were also the most common complaints a few days after treatment and when physical clinical examination was repeated three months after treatment.

Analysis of these symptoms before, and three months after treatment (Table 7) shows that fewer children had complaints after treatment than before. Particularly noticeable is the virtual disappearance of blood in the stools after

treatment. Complaints of abdominal pains were variable in that slightly more children who had received one day's treatment had this complaint after treatment than before, whereas fewer children had this complaint after receiving treatment for two days.

The commonest physical finding was enlargement of the liver — up to 10 cm below the costal margin. A few children had enlarged spleens.

As shown in Table 8, there appears to have been regression of liver enlargement three months after treatment.

These symptoms and signs have not, however, been analysed as they applied to each child in the follow up and, therefore, no statistical analysis can be applied.

TABLE 8. Hepatic and splenic measurements before and three months after treatment.

Regimen of treatment	15 mg/kg b.d. for 2 days	10 mg/kg b.d. for 2 days	15 mg/kg b.d. for 1 day
Treatment			
Nos. examined	31	32	50
Enlarged spleen Nos. (%)	2 (6.5)	0 (0)	0 (0)
Enlarged liver Nos. (%)	15 (48.4)	17 (53.1)	28 (56)
3 months post-treatment			
Nos. examined	25	26	4
Enlarged spleen Nos. (%)	0 (0)	0 (0)	1 (2.3)
Enlarged liver Nos. (%)	5 (20)	2 (7.7)	14 (31.8)

These data cannot be subjected to critical statistical analysis because they do not refer to the same patients.

Discussion and Conclusion

The cure rates and egg reduction rates obtained in *Schistosoma mansoni* infestation, i.e., 93.3% and 99%, respectively, at three months after treatment,

compare favourably with any other drug therapy; they are in fact higher than in other current therapy.

After a period of three months it is generally considered that the appearance

of ova in the stools may not only reflect ineffectiveness of treatment but also new infestations with the worm, if the patient has remained in the same endemic environment.

In this trial, the children remained in the same endemic environment which was not disturbed in any way. Follow-up nine months after treatment showed an overall cure rate of 93.7%, which is about the same as the rate obtained in the follow-up three months after treatment. However, only about half of the children were followed up for nine months and therefore no definite conclusions can be drawn from this comparison. It would seem, though, that the apparent cure rate was maintained in this area with little or no new infestations with *S. mansoni*. Perhaps thorough epidemiological studies of the disease in this area combined with controlled trials would clarify the situation.

To a small extent, the rather high readings obtained in various haematological and biochemical parameters, serum SGPT, SGOT and bilirubin are due in part to the fact that there was a delay of up to 24 hr in separating the serum from the blood specimens which resulted in some haemolysis; but this applied to all the specimens and cannot explain the difference noticed in values obtained before and after treatment.

Some of the increases in the levels of alkaline phosphatase, bilirubin, haemoglobin and WBC after treatment, though they do not show any statistically significant difference in SGOT and SGPT, have also been noticed by other workers.

One explanation which has been advanced is that the increase in WBC is due to reactions by the host to dead worms or their constituents. But this has not been proved and no satisfactory explanation has been advanced for other parameter increases. However, the fact that these levels do not exceed normal values leads one to suspect that the patients did not experience untoward effects as a result of this treatment.

The side effects of drowsiness, nausea, vomiting, headache and abdominal pain have also been noted by other workers but were all mild and did not interfere with the children's activities. It is difficult to decide whether the complaints of abdominal pain and headache should be regarded as side effects or not, as they were also frequently complained of by children before and after treatment.

Although the symptoms and clinical findings have not been subjected to critical statistical analysis as they have not been strictly analysed for each child, the symptoms complained of by children before treatment such as passing bloody stools (Table 7) are much less frequent after treatment, and hepatosplenomegaly is also less. These items undoubtedly require more statistical observation in future trials.

Our results show Oxamniquine to be more effective and more easily administered and tolerated in the treatment of *S. mansoni* infections than other currently available drugs. Oxamniquine deserves to be tried in community control programmes combined with other measures.

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OXAMNIQUINE IN THE TREATMENT OF SCHISTOSOMA MANSONI INFECTION IN EGYPT

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Oxamniquine is a recently introduced non-antimonial compound which was found to be of remarkable schistosomicidal activity (Pellegrino and Katz, 1972 ; Foster, 1972). It is a tetrahydroquinoline derivative which is obtained through the hydroxymethylation of 2-aminomethyl tetrahydroquinoline.

Our experience with this drug started a few years ago when we tried it by the intramuscular route, for a possible single-dose parenteral therapy of bilharziasis, and also so as to determine its safety and tolerability for human use. We started at that time with a dose range of 1.0-8.0 mg/kg of body weight in *Schistosoma haematobium* infection and up to 10 mg/kg b.w. in *S. mansoni* infection. But in either infection the results proved to be unsatisfactory. Besides, the higher doses caused considerable local pain and induration.

Then we tried it by the oral route in a total dose range of 20-60 mg/kg b.w. in 1-3 days for the treatment of *S. haematobium* infection, but the results were disappointing. On the other hand, no conspicuous side effects were noticed during its oral administration. With regard to its safety, full haematological investigations, liver function tests (serum bilirubin, serum glutamic pyruvic transaminase, serum glutamic oxalacetic transaminase, and serum alkaline phosphatase), kidney

function tests (urine analysis, endogenous creatinine clearance and urea clearance), as well as electrocardiographic tracing, did not show any conspicuous changes when they were carried out before and weekly after treatment for one month.

We recently tried oxamniquine for the treatment of *S. mansoni* infection in a total dose range of 20-60 mg/kg b.w. till we reached a satisfactorily effective dose level of 60mg/kg b.w. divided on three consecutive days.

The present work demonstrates our results with this latter dose.

Material and Methods

In order to obtain comparable and dependable results we preferred to carry out the trial on a group of male patients having approximately the same age and weight. To this end we chose *S. mansoni* cases from among newly recruited policemen in the age range of 20-25 years. The patients were otherwise clinically free from any organic disease and the stools were positive for living *S. mansoni* ova.

The patients were given oxamniquine in the daily oral dose of 20 mg/kg b.w. for three consecutive days.

Ova counts were carried out before treatment and thereafter monthly for the period of three months, using a modification of Bell's (1963) technique. More-

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over, the hatching test was carried out together with the last ova count.

Results

Up till now, 23 of the treated cases have completed the follow up period of three months. Results show that only four cases were still positive by both ova counts and by the hatching test, i.e., 17.4% ; three of them had an ova reduction of 90-70%.

All the other cases, i.e., 82.6%, were persistently negative by the hatching test. Of these, 14 cases had a 100% ova reduction (60.9% of the 23 cases), the rest having an ova reduction of 96-99% except for one who had an ova reduction of 72.7%. The last case had been previously negative by ova counting in the first and second months of follow up.

Conclusions

In our studies on this compound, we found that it is effective in the treatment

of *S. mansoni* infection but not in *S. haematobium* infection, at least in the dose schemes we applied up to now. It is to be noted that the promising total dose in our cases is higher than that found effective elsewhere. This may be due to difference in the worm strain. Moreover the drug was well tolerated and our previous studies proved it to be safe to use in man.

In this dose, and in the relatively small number of controlled cases followed up till now for the period of three months, the cure rate by the hatching test was 82.6%. 60.9% of all the followed up cases were negative by both hatching and ova counting and the remainder of the negative cases (except for one) had an ova reduction of 96-99%.

This denotes that the drug shows promise in the effective treatment of *S. mansoni* infection.

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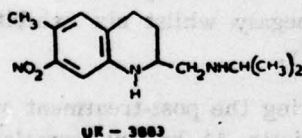
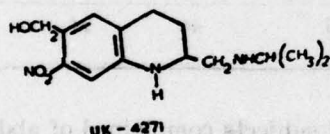
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OXAMNIQUINE (UK 4271) IN THE TREATMENT OF SCHISTOSOMA MANSONI INFECTIONS IN UGANDA

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Oxamniquine (UK-4271) is a new antischistosomal drug mainly effective against *Schistosoma mansoni*. It is a tetrahydroquinoline derivative with the chemical name 6-hydroxymethyl-2-isopropylaminomethyl-7-nitro - 1,2,3,4-tetrahydroquinoline and is obtained by hydroxylation of a sister compound 2-isopropylaminomethyl-6-methyl-7-nitro - 1,2,3,4-tetrahydroquinoline also known as UK-3883.



It has already undergone clinical trials in S. America (Foster, 1974), S. Africa (Fripp, 1973), Tanzania (Eyakuze & Rugemalila, 1974) and Kenya (Siongok et al., 1975) where preliminary reports indicate a high efficacy by both parenteral and oral administration. Because pain at the site of injection has often proved excruciating with an accompanying induration, intramuscular administra-

tion of the drug is no longer considered ideal (Eyakuze & Rugemalila, 1974).

In this paper we describe the use of Oxamniquine in the treatment of *S. mansoni* at a clinic in Kampala, the capital of Uganda, and in Pakwach, a highly endemic area of *S. mansoni* (300 km to the north of Kampala) (Ongom & Bradley, 1972), by oral administration of the drug.

Materials and Methods

The efficacy and side effects of Oxamniquine could not be assessed, either at Kampala, where the population is generally mobile and follow-up becomes extremely difficult, or at Pakwach where, though the population is stable, it is rather reluctant to submit to investigations involving venepunctures (Ongom, 1969). Hence the Kampala clinic (located within the Institute of Public Health) was used to assess, mainly, the effects of the drug on the haematologic picture, and on liver and renal function, whilst Pakwach was used to assess the efficacy of the drug in the elimination of the parasites from human host reservoirs.

At Kampala cases of *S. mansoni* referred to the authors had stool egg counts done by the MIF technique: blood was taken for determining haemoglobin, mean corpuscular haemoglobin, packed cell

volume, erythrocyte sedimentation rate, white blood cells (total and differential), urea, bilirubin, alkaline phosphatase, serum glutamic oxalacetic transaminase (SGOT) and total protein levels. Urine specimens were also requested and analysed for specific gravity, pH, protein, sugar and deposits. Subjects were then randomly and alternately allocated to either treatment A (10 mg/kg body weight twice daily for two days) or B (15 mg/kg body weight twice daily for one day) in the form of capsules in denominations of 500, 250, 125, 50 and 25 mg. Children were given the syrup form of the drug containing 50 mg/ml.

Three to four days after treatment patients were reviewed and any significant side effects attributable to the drug noted. Post-treatment specimens of blood and urine were taken and the above investigations were repeated. Provided subjects were available, coprological examinations were generally carried out one month after treatment.

A few people (six male subjects) were also treated with the parenteral form of the drug (I/M injection at 7.5 mg/kg body weight given as a single dose); results of this regime are excluded.

At Pakwach pre- and post-treatment coprological egg-counts (1, 3, 6 and 9 months after treatment) were carried out using the same technique. The same dosages and regimes of treatment were applied as in Kampala. Post-treatment reviews of patients for side effects were carried out 3-5 days later.

Results

At Kampala a total of 70 patients (46 males and 24 females) were treated and reviewed. The majority were between 5-34 years old (Table 1). Most subjects (45) belonged to the Jonam/Alur tribe

and next in frequency came the Lubhbara/Kakwa (15). Both communities come from known endemic areas of *S. mansoni* in the Nile Province. A few people representing the Madi, Acholi, Lango, Sudanese and Samia tribes were also included in the study.

TABLE 1. Age distribution of 70 patients at Kampala.

Age group (years)	Males	Females	Total
2 — 4	1	—	1
5 — 9	5	3	8
10 — 14	3	6	9
15 — 19	5	5	10
20 — 24	12	2	14
25 — 29	10	3	13
30 — 34	8	2	10
35 — 39	1	—	1
40 — 44	1	—	1
45 +	—	3	3
Total	46	24	70

All subjects complained of abdominal pain, a few of diarrhoea; 11 of them had hepatomegaly whilst six exhibited splenomegaly.

During the post-treatment survey of the subjects, 11 had no complaints, 47 complained of dizziness lasting between $\frac{1}{2}$ -3 hr and in a few cases patients were drowsy for several hours and complained of what they described as 'being drunk'. There were six cases of vomiting and four of nausea. One subject expelled segments of *Taenia* soon after the administration of the drug. Some subjects complained of abdominal pain and diarrhoea, but these symptoms can be ignored, since they were the main symptoms in these subjects before treatment (Table 2).

TABLE 2. Side effects among 70 patients in Kampala upon treatment with Oxamniquine.

Side effect	Number
None	11
Dizziness	47
Nausea	4
Vomiting	6
<i>Taenia</i> in stool	1

Liver Function Tests before and after treatment remained the same in nearly all cases. Blood urea, serum bilirubin and serum alkaline phosphatase were considered raised in one instance each after treatment with oxamniquine. SGOT was raised in two cases. A few urinary casts appeared after treatment in four cases (including one of red blood cells in the subject who had raised serum bilirubin). Insignificant albumin traces appeared in the urine after treatment in one case only. The haematological picture remained normal after treatment in all cases. Table 3 shows the reduction in eggs in 27 cases in which faecal egg-counts were made before, and one month after treatment. Excretion of eggs was quite markedly reduced. Only in a single case was the reduction in the egg-count only 40%.

TABLE 3. Reduction in egg excretion in 27 patients in Kampala examined one month after treatment.

Egg Reduction	Nos.
100%	21 (77.7% cured)
99%	3
96 — 98%	1
95%	2
Total	27

A comparison of the cure rates of the two regimes of treatment for people treated at Kampala is shown in Table 4.

TABLE 4. Comparison of cure rates with different treatment regimes in Kampala one month after treatment.

Regime	No. treated	No. cured	% cured
A	12	10	83.3
B	15	11	73.3

At Pakwach a total of 76 patients (40 males and 36 females) were treated (Table 5) and at 1, 3, 6 and 9 months after treatment 71, 52, 39 and 45 subjects respectively had faecal egg-counts done (Table 6). All subjects were Jonam and came from the village of Panyagoro, Pakwach Nile Province, Uganda.

TABLE 5. Age distribution of 76 patients at Pakwach.

Age	Male	Female	Total
5 — 9	9	9	18
10 — 14	23	9	32
15 — 19	1	2	3
20 — 24	1	3	4
25 — 29	4	3	7
30 — 34	—	4	4
35 — 39	—	1	1
40 — 44	—	1	1
45 +	2	4	6
Total	40	36	76

TABLE 6. Cure rates in Pakwach at various times after treatment.

Time after treatment	No. examined	No. cured	% cured
1 month	71	59	83
3 months	52	18	34.6
6 months	39	13	33.3
9 months	45	16	35.5

A further comparison of cure rates of treatment regimes A and B is made in Table 7. The comparison refers only to the egg-counts made one month after treatment.

TABLE 7. Comparison of cure rates in the two regimes used at Pakwach one month after treatment.

Regime	No. treated	No. cured	% cured
A	36	33	91.6
B	40	31	77.5

Before treatment, all subjects, at one time or another, complained of abdominal pain and diarrhoea with or without blood. On examination at least 40 subjects had either hepatosplenomegaly, or hepatomegaly alone, or splenomegaly alone (Table 8).

TABLE 8. Distribution of hepatic and splenic enlargement in 40 cases at Pakwach.

Hepato-splenomegaly	Hepato-megaly	Spleno-megaly	Total
15	11	14	40

Of the total number (76) of subjects treated, 53 were interviewed, and some were also observed, for side effects. There were 16 subjects who reported they had felt no side effects. Many (28) complained of dizziness which ranged from light, and lasting only half an hour, to severe, and lasting for several hours. In a few cases dizziness resulted in serious drowsiness, which was sometimes described as «drunkenness». There were five cases of vomiting, one of which brought up *Ascaris*. Hookworms were passed out in two cases following the administration of

oxamniquine and another subject passed out *Ascaris*. *Taenia* segments were passed in one case (Table 9). Many subjects reported a yellow coloration of the urine and stools during the administration of the drug.

TABLE 9. Side effects among patients treated at Pakwach.

Side effects	Number
None	16
Dizziness	28
Vomiting	4
Vomiting <i>Ascaris</i>	1
Hookworms in stool	2
<i>Taenia</i> in stool	1
<i>Ascaris</i> in stool	1

There were also many cases who reported abdominal pain and diarrhoea, but these, as in the case of the Kampala study group, were ignored, since both symptoms were predominant in the community at any time.

In all cases cure was established as a result of a negative hatching test.

Discussion

Ideally, a good antischistosomal drug, and for that matter any anthelmintic, is one whose active principle is selective and concentrates on the parasite alone without toxic effects on the host. In practice this is hardly ever achieved. Conventional antischistosomal drugs currently in use are either too toxic to the host (antimony compounds) or ineffective in the elimination of the parasites (Lucanthone hydrochloride). Newer preparations all have their disadvantages: niridazole has very

little effect on *S. mansoni* and is now alleged to be an immunosuppressive agent; metrifphonate has some moderate effects on *S. haematobium* only; and hycanthone, though powerful against schistosomes, has unwarranted side effects and hence is contraindicated in many instances including hepatosplenomegaly, which almost excludes its use in major endemic areas.

Oxamniquine, a drug with special affinity for *S. mansoni*, is one of the new candidates in the fight against schistosomiasis. But it is not without some of the disadvantages of its predecessors, the main one being a temporary dizziness which, however, is negligible in the younger age-groups and when the drug is taken after meals. Its potency is claimed to be much higher than that of hycanthone, niridazole and lucanthone; it was shown, in rodents, to act primarily on male schistosomes, mainly causing their migration to the liver; in the female worm it temporarily interfered with the egg-laying mechanism (Foster & Cheetham, 1973).

In other experimental animals, in which it caused the death of male worms, a large number of females survived; egg laying was not resumed for at least six months (Foster, Cheetham & King, 1973).

In areas endemic for schistosomiasis complete chemotherapeutic cure is not an end in itself, as re-infection must occur. Hence drugs are considered only as an aid to general control measures, a fact widely accepted today (WHO, 1972).

Of the two regimes of treatment, that with 10 mg/kg body weight twice daily for two days (Regime A) has produced better cure rates both at Kampala and Pakwach. At Pakwach the difference reaches statistical significance ($P = 0.1$), as the Mann-Whitney U-Test fails to re-

ject the similarity in the distributions of the initial egg-counts for the two groups of patients. Also, there were many more eggs produced by the Regime B group at the one month post-treatment period than for the Regime A group.

The effect of oxamniquine on other helminths, such as *Ascaris*, hookworms and *Taenia* needs further investigation. However, it is already known that potent drugs in the treatment of *Ascaris*, such as piperazine hydrochloride, which belongs to the same chemical class as oxamniquine, have conferred some protection against *S. mansoni* infections in experimental studies (Mousa et al., 1968).

Whilst the main side-effect of oxamniquine remains dizziness, lack of obviously serious adverse effects on hepatic and renal functions remains an asset to test its credibility in mass chemotherapy in conjunction with other antibilharzial measures during a pilot control project.

Summary

Oxamniquine (UK-4271), a new anti-schistosomal drug, was used in the treatment of *S. mansoni* in Uganda. Cure rates of 83.3% and 91.6% were obtained with an oral dose of 10 mg/kg body weight twice daily for two days, whilst 15 mg/kg body weight twice daily for one day gave cure rates of 73.3% and 77.5% at Kampala and Pakwach respectively.

The main side effect was dizziness but there were no noticeable effects on the haematologic picture, and hepatic and renal functions remained undisturbed. The drug appears to exert adverse effects on other helminths such as hookworms, roundworms and tapeworms.

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CLINICAL TRIALS OF ORAL OXAMNIQUINE IN SCHISTOSOMIASIS IN MWANZA, TANZANIA

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Preliminary clinical trials in Africa by Clarke et al. (1973), Eyakuze (1973), and Rees et al. (1973), and in South America by Coutinho et al. (1973), Katz et al. (1973), and several other workers, have shown that oxamniquine is very effective in *S. mansoni* infections and less so, or not at all, in those with *S. haematobium*. The intramuscular formulation causes severe pain and induration at the injection site. Early unpublished trials by the authors with a single dose of the oral formulation gave as good egg reduction rates as the parenteral preparation, but lower cure rates (see Table 1). The lower cure rates were attributed by some workers to giving the oral formulation after meals. The objectives of the series of trials reported here were to determine the optimum oral dosage for *S. mansoni* infections, to reassess its effects on *S. haematobium* infections, and to determine the time when egg excretion stops after treatment.

Materials and Methods

Screened patients residing in an endemic area and excreting *S. mansoni* or *S. haematobium* eggs were admitted to hospital in small groups for supervised treatment. Pre-treatment examinations included quantitative estimation of egg output by the filtration-staining method, and haematological and biochemical tests by standard methods. Oxamniquine was administered as capsules or as syrup in doses ranging from 10 to 20 mg per kg

body weight, at least one hour before meals. The patients were observed closely for side effects in hospital and discharged on the third day after taking blood for biochemical and haematological tests. At follow-up 30 and 60 days after treatment, biochemical and haematological tests were repeated, and 24-hr stool (in *S. mansoni*) or midday urine (in *S. haematobium*) was examined for eggs by the filtration-staining and miracidial hatching tests. The criterion for cure was a negative miracidial hatching test. In an attempt to determine the time when egg excretion stops, a small number of patients treated with 12.5 mg/kg twice daily for one day had their stools examined by the filtration-staining and miracidial hatching tests daily for seven weeks after treatment.

Results

The effects of treatment by the various dose regimens were studied in 103 patients with *S. mansoni* and 25 with *S. haematobium* infections. The side effects observed, their incidence, and tolerance of the drug are shown in Table 2 and the haematological and biochemical effects in Tables 3 and 4 respectively. Tables 5 and 6 give the parasitological effects of the drug at different doses in *S. mansoni* and *S. haematobium* infections. Figure 1 demonstrates daily egg output and viability in *S. mansoni* infections following treatment.

TABLE 1. Parasitological results of single oral doses of oxamniquine given after meals in *S. mansoni* infections.

Group	No. pts.	Initial mean eggs/g	Dose (mg/kg)	% Egg reduction			% Cure rate		
				1 mo	2 mos	3 mos	1 mo	2 mos	3 mos
1	10	48	10 b.d. \times 1 day	81	85	44	22	30	44
2	9	99	15 b.d. \times 1 day	99	91	86	44	22	29
3	9	151	20 b.d. \times 1 day	94	51	83	11	11	25

(*) b.d. = twice a day.

TABLE 2. The side effects observed, their incidence rates, and tolerance of the drug according to dosage.

Side Effects	Percent Incidence Rate					
	12.5 bd, 2 days	12.5 bd, 1 day	15 bd, 2 days	15 bd, 1 day	20 bd, 1 day	
Somnolence	9	80	100	80	91	
Dizziness	0	70	27	10	27	
Headache	9	0	9	0	18	
Nausea	9	20	18	0	9	
Vomiting	0	10	9	0	9	
No side effect	82	9	0	0	0	

TABLE 3. Haematological effects on patients treated for *S. mansoni* and *S. haematobium* infections.

(Normal values)	Haemoglobin (14-16g/100 ml)						Total WBC $\times 100$ (61.0 $\times 100$ /ml)						Neutrophil (41%)					
	0	3	30	60	0	3	30	60	0	3	30	60	0	3	30	60	0	3
Days post-treatment																		
Mean values																		
<i>S. mansoni</i>	11.8	9.1	11.7	11.3	58.3	51.5	61.7	58.0	39	42	37	36						
<i>S. haematobium</i>	11.6	11.5	10.4	10.9	54.6	52.0	63.0	53.0	39	41	36	30						
<i>S.m. + S.h.</i>	11.7	10.2	11.1	11.0	56.4	51.7	62.7	55.0	39	41	36	33						
No. examined																		
<i>S. mansoni</i>	24	24	25	24	24	24	25	23	24	24	25	23						
<i>S. haematobium</i>	24	22	25	24	24	23	25	24	25	23	25	24						
Total	48	46	50	48	48	47	50	47	49	47	50	47						

TABLE 4. Biochemical effects on patients treated for *S. mansoni* and *S. haematobium* infections.

(Normal values)	S G P T (2-15 I.U./litre)				Alkaline phosphatase (5-10 K.A.U./100 ml)			
Days post-treatment	0	3	30	60	0	3	30	60
Mean values								
<i>S. mansoni</i>	4.2	3.5	3.1	3.8	12	12	16	14
<i>S. haematobium</i>	3.5	4.2	3.9	5.2	14	12	13	9
<i>S.m.</i> + <i>S.h.</i>	3.9	3.7	3.5	4.5	13	12	14	12
No. examined								
<i>S. mansoni</i>	30	28	24	21	30	28	22	21
<i>S. haematobium</i>	23	18	25	23	23	18	24	21
Total	53	46	49	44	53	46	46	42

I.U. = international units.

K.A.U. = King-Armstrong units.

TABLE 5. Parasitological results according to dosage of oral oxamniquine in *S. mansoni* infections.

Regimens	Dose (mg/kg)	No. of pts.	Initial mean eggs/g		% Egg reduction		% Cure rates	
			Mean	Variance	1 mo	2 mos	1 mo	2 mos
A	12.5 bd, 2 days	11	59	4,441	98	95	36	0
B	12.5 bd, 1 day	24	22	436	98	99	77	73
C	15 bd, 2 days	22	79	29,573	99+	99	91	82
D	15 bd, 1 day	8	18	656	99	100	100	88
E	20 bd, 1 day	10	47	3,858	95	96	50	20
Overall		75	47	10,148	98	98	74	59

TABLE 6. Parasitological results according to dose of oral oxamniquine in *S. haematobium* infections.

Regimens	Dose (mg/kg)	No. of pts.	Initial mean eggs/10ml.	% Egg reduction		% Cure rate	
				1 mo	2 mos	1 mo	2 mos
F	10 bd \times 3 days	14	250	79	76	0	7*
G	20 bd \times 3 days	11	280	37	52	9	9*

(*) Single patient showing negative hatching test.

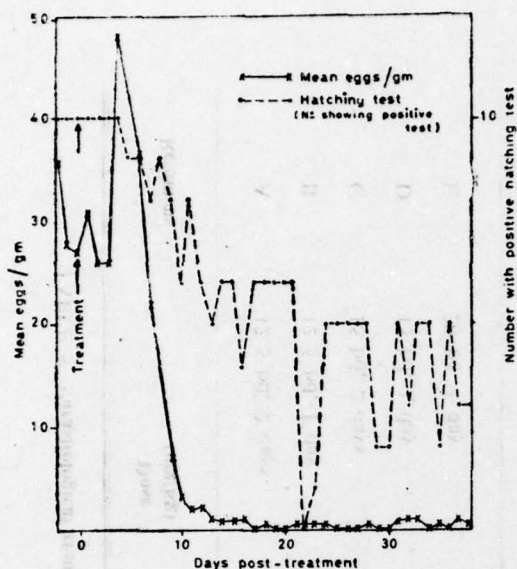


Fig. 1. Effect of oral oxamniquine on egg excretion and hatching test in *Schistosoma mansoni* infection.

Discussion

The side effects which were observed are somnolence, dizziness, headache, nausea, and vomiting. Other complaints like abdominal pain and diarrhoea were ignored since these are either known intermittent symptoms of *S. mansoni* infections, or common mild complaints among the patients' community. All side effects were mild and transient; somnolence and dizziness, which were most frequent were dose-related, an observation also reported by Siongok et al. (1975). The side effects observed in this study compare with those reported by other workers in East Africa as shown in Table 7.

Haematological tests showed a transient fall in total leucocytes at three days, followed by a rise mainly due to eosinophils at 30 days, and a moderate neutropenia at 30 and 60 days. There was a rise in the mean alkaline phosphatase level in *S. mansoni* infections, the rise being higher in subjects below 20 years of age.

Both haematological and biochemical changes were neither constant nor statistically significant. However, changes of the same order have been reported by Siongok et al. (1975).

In *S. mansoni* infections every dose used reduced egg excretion by 90 to 100%. The cure rates achieved by regimens B, C, and D were 70-100% (see Table 5). These cures did not differ significantly by the Chi-square test ($p > 0.05$), even though the pre-treatment egg counts were not comparable by the 't' test ($p < 0.05$). Ongom et al. (1975) reported a similar observation on two groups of patients who also had incomparable initial egg counts, but showed similar cure rates when treated with the same dosage of oral oxamniquine. Table 8 compares our cure rates with those reported by other workers; the rates should be compared with caution because of the differences in the criteria of cure.

From the observations made on the patients whose stools were examined daily for *S. mansoni* eggs following treatment (see Fig. 1), oral oxamniquine seems to stimulate egg excretion for a day or two; it then rapidly falls off within 10 days. Between 10 and 20 days a few eggs continue to be excreted but from day 20 onwards hardly any eggs are detectable. Similarly the hatching test is negative, by about day 20, in all those who are going to be negative, so that maximal drug effect, or cure, can be said to have occurred three weeks after treatment with this drug.

In *S. haematobium* infections oral oxamniquine in doses of 10 mg/kg twice daily or 20 mg/kg once daily for three days produced poor egg reduction and hardly any cures at all. This is in spite of the high total dosage of 60 mg/kg which is twice as high as the maximum

TABLE 7. Comparison of unwanted effects of oral oxamniquine reported by various workers.

Authors	Dosages (mg/kg)	Side effects	Haematology	Biochemistry
Siogok <i>et al.</i> (1975)	10bd × 2 days 15bd × 1 day 15bd × 2 days	1. Drowsiness 2. Headache 3. Abd. pain 4. Nausea 5. Vomiting	1. Leucocytosis	1. Rise in alk. phosphatase 2. Rise in SGPT
Ongom <i>et al.</i> (1975)	10bd × 2 days & 15bd × 1 day	1. Dizziness 2. Drowsiness 3. Vomiting 4. Nausea	Normal	Essentially normal
Eyakuze & Rugemalila (1975)	12.5bd × 2 days 12.5bd × 1 day 15bd × 2 days 15bd × 1 day 20bd × 1 day	1. Somnolence 2. Dizziness 3. Headache 4. Nausea 5. Vomiting	1. Leucocytosis 2. Neutropenia	1. Rise in alk. phosphatase

TABLE 8. Comparison of parasitological results of oral oxamniquine in *S. mansoni* infections as reported by various workers.

Authors	Dosage (mg/kg)	No. of pts.	Initial Mean eggs/g	% Egg reduction	% Cure rate	Time and criterion of cure
Ongom <i>et al.</i> (1975)	10bd, 2 days	36	—	—	91	1 month, Negative H.T.*
	15bd, 1 day	40	—	—	78	1 month, Negative H.T.
Siongok <i>et al.</i> (1975)	10bd, 2 days	32	981	100	100	2 months, Absence of eggs
	15bd, 1 day	60	671	99	94	2 months, Absence of eggs
	15bd, 2 days	31	937	100	100	2 months, Absence of eggs
Eyakuze & Rugemalila (1975)	12.5bd, 1 day	24	22	99	73	2 months, Negative H.T.
	15bd, 1 day	8	18	99	88	2 months, Negative H.T.
	15bd, 2 days	22	79	99	82	2 months, Negative H.T.

(*) H.T. = hatching test.

dose given in *S. mansoni*. This poor effect of oxamniquine on *S. haematobium* was also noted by the manufacturers, and by Clarke et al. (1973).

For the treatment of *S. mansoni* infections, oral oxamniquine compares favourably with niridazole whose cure rates range between 40 and 75% (WHO, 1972). Oxamniquine has the added advantages of having milder side effects and providing a shorter course of treatment. A dose of 12.5-15 mg/kg taken twice daily for

one day before meals seems to be adequate. The lower dose (12.5 mg/kg) minimises the side effects but gives nearly the same egg reduction and cure rate as the higher dose, and is thus preferable.

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SEMI-MASS TREATMENT OF URINARY BILHARZIASIS WITH METRIFONATE

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Previous extensive studies in Egypt (Saif et al., 1973) proved the efficacy of metrifonate in the treatment of urinary *Schistosoma haematobium* infection at an oral dose of 10 mg/kg b.w. every two weeks for three doses. This dose regimen was reported to be well tolerated with no conspicuous side-effects or toxic reactions. Compared to other antibilharzial compounds, metrifonate was found to be more than satisfactory from all aspects in the treatment of urinary *S. haematobium* infection (Saif et al., 1974). Besides even in cases of failure, the post-treatment percentage reduction in ova was remarkable (Saif et al., 1973, 1974).

These results stimulated the trial of this compound on a semi-mass basis in order to assess its validity for mass treatment schemes, which is the subject of the present work.

Material and Methods

308 adult male patients in the age range of 21-25 years, suffering from active urinary bilharziasis, were the material of the present study. The urine samples of all of them contained living *S. haematobium* ova. All reported to have had no previous antibilharzial treatment for at least one year prior to the present investigation.

Each individual was given metrifonate orally in the form of 100 mg

tablets, at a dose of 10 mg/kg b.w. every two weeks for three doses. In order to avoid the occurrence of any possible side effects, the drug was administered 2 hr after breakfast instead of on an empty stomach. The drug was administered to the patients while they were actively at work.

The urine of each patient was examined microscopically for bilharzia ova before the administration of the second and the third doses and then six months after the third dose for final assessment of the results of treatment.

For follow-up purposes, the pipetted urine deposit, obtained by simple sedimentation in a conical glass, was examined. When negative, examination was repeated after centrifugation. If still negative, a third sample of urine was obtained after muscular exercise and was re-examined for ova after centrifugation.

Side effects were ascertained by indirect questioning in order not to obtain any misleading answers.

Results

Out of the 308 patients 39 (12.7%) proved negative two weeks after the first dose. Two weeks after the second dose the number of negatives rose to 291 (94.5%). Six months after the third and last dose 285 patients could be duly followed up, of whom 265 proved to be per-

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sistently negative (93.0%). The remaining 23 patients were unable to attend for the final follow-up, due to their transfer for employment in areas far away from the treatment unit, but they reported to be in good physical condition.

No conspicuous side-effects or toxic reactions could be observed in any of the treated patients, and the compound was well tolerated. Moreover, its administration was carried out while the patients were at work, without the need for any particular measures or restrictions.

Conclusions

The results obtained in the present work denote that metrifonate is a dependable, highly effective, safe and well tolerated antibilharzial compound that can be introduced for the effective mass treatment of urinary *S. haematobium* infection.

Summary

Metrifonate, in the oral dose of 10 mg/kg b.w. 2 hr after breakfast every two weeks for three doses, was found to give a cure rate of 93.0% in urinary *S. haematobium* infection, after a follow-up period of six months. No side-effects or toxic reactions were reported. The drug was found to be well tolerated when given to ambulant patients while at work, physical rest not being required. It is recommended for mass treatment of urinary *S. haematobium* infection, being highly effective, safe to use, well tolerated and easily applicable to ambulant cases without any particular conservative measures.

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MASS SHORT-TERM TREATMENT OF URINARY BILHARZIASIS WITH NIRIDAZOLE : A FIELD TRIAL

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The use of niridazole at a daily oral dose of 25 mg/kg b.w. for 5-7 days was found to be remarkably effective in the treatment of both urinary and intestinal bilharziasis. But this course of treatment was found to be frequently associated with some side effects which sometimes resulted in the interruption of treatment, especially in the longer dose regimen (Abdallah et al., 1966 ; Abdallah et al., 1968 ; Abdallah & Saif, 1969). Such side effects usually occurred by or after the fourth day of treatment. This led some workers to try the same daily dose of the compound for only three consecutive days. They reported the latter scheme of treatment to be promising for the large scale treatment of bilharziasis (Saif et al., 1974).

This stimulated us to try this short course of treatment with niridazole in a pilot field study, in order to assess its efficacy, tolerability and safety in the mass treatment of urinary bilharziasis, as well as its effect on the overall prevalence of the disease in the community treated.

Material and Methods

For the present trial, a village near Cairo was chosen in which no control measures for schistosomiasis had been undertaken. It had a population of 6194. According to a mass investigation comprising 4681 inhabitants, i.e., 75.6% of the population of the village, the 1972

prevalence rate assessment for *Schistosoma haematobium* infection was 25.78%. In 1973, before the start of the present study, 4078 individuals could be investigated to ensure the stability of the base-line data and the prevalence rate of urinary bilharziasis was found to be 25.06% (Table 1).

TABLE 1. Sequential prevalence of *Schistosoma haematobium* infection in the village.

Year	No. examined	+	%
1972	4681	1207	25.78
1973	4078	1022	25.06
1974	3925	506	12.89

All of the 1022 positive cases detected in the 1973 survey (Table 1) were subjected to treatment with niridazole at a daily oral dose of 25 mg/kg b.w. for three consecutive days.

Urine samples were examined for ova by microscopical examination of the sediment which was pipetted off after the urine sample had been left in an inverted cone glass container for $\frac{1}{2}$ hour.

Results

Only 887 cases regularly attended the course of treatment (86.83%) ; the rest

did not complete the course through personal negligence, as evidenced by thorough investigation and a questionnaire for the possible occurrence of any side effects. Out of the 887 individuals who completed the course of treatment, only 668 cases could be followed up after three months (75.3%), of whom 589 cases were found to be negative (88.2%). Of the 589 negative cases, 542 cases could be traced for up to six months, of whom 515 cases (95.02%) were found to be negative. After the lapse of one year, 250 out of the 515 negative cases were taken at random for re-examination; of these 237 cases were found to be still negative, i.e., 94.8% (Table 2).

TABLE 2. — Follow up of treated cases.

Follow up period	No. of cases	% negative
3 months	668	88.20
6 months	542	95.02
12 months	250	94.80

By the end of 1974, another comparative mass survey was carried out in the village on 3925 individuals, covering 63.4% of the whole population and 96.3% of those surveyed in 1973. It revealed an over-all prevalence rate of 12.89% for urinary bilharziasis (Table 1).

Further, prevalence rates were also studied in school children during three roughly corresponding periods, i.e., during the school years 1972/1973, before the institution of treatment; in 1973/1974, after treatment, and in 1974/1975, nearly 15 months after treatment. Details are shown in Table 3. The overall results denote consecutive drops in the prevalence rate of urinary bilharziasis in these young age groups from 20.2% to 10.2% and 9.9%.

TABLE 3. — Bilharziasis infection among school children of the village.

Age group (years)	Scholastic year					
	1972/1973		1973/1974		1974/1975	
	No. of cases	% +	No. of cases	% +	No. of cases	% +
6-7	117	10.3	107	4.7	53	1.9
7-8	170	12.9	123	6.5	105	3.8
8-9	148	9.5	95	12.6	92	9.8
9-10	109	35.8	72	18.1	88	19.3
10-11	85	32.9	51	13.7	73	11.0
11-12	50	44.0	43	11.6	94	11.7
Total	679	20.2	491	10.2	505	9.9

Conclusions

The short course of niridazole in the daily oral dose of 25 mg/kg b.w. for three consecutive days proved to be a safe and well tolerated, as well as effective, regimen for the mass treatment of urinary bilharziasis. Moreover, it resulted in the overall lowering of the prevalence rate of the disease despite the absence of any

other control measures. Side effects were minimal.

Acknowledgements : Thanks are due to Dr. M. Saif, Director General, Institute of Research for Tropical Medicine, for his valuable supervision and advice. Thanks are also due to the CIBA-GEIGY Scientific Office for the provision of the material necessary for this study.

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**COLONOSCOPY IN EVALUATING THE EFFECT OF NIRIDAZOLE
TREATMENT ON SCHISTOSOMAL COLONIC POLYPOSIS**

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This study represents a collaborative work between NAMRU-3 and Professor Dr. Abu Shady El-Rooby, Tropical Medicine Department, Kasr El Ainy University Hospital, Cairo.

The study consists of two parts (1) short term post-treatment follow up and

(2) long-term post-treatment follow-up (about five years).

Colonic polyposis is a common complication of schistosomiasis in Egypt and is seen in more than 20% of Egyptians with this disease (Fig. 1).

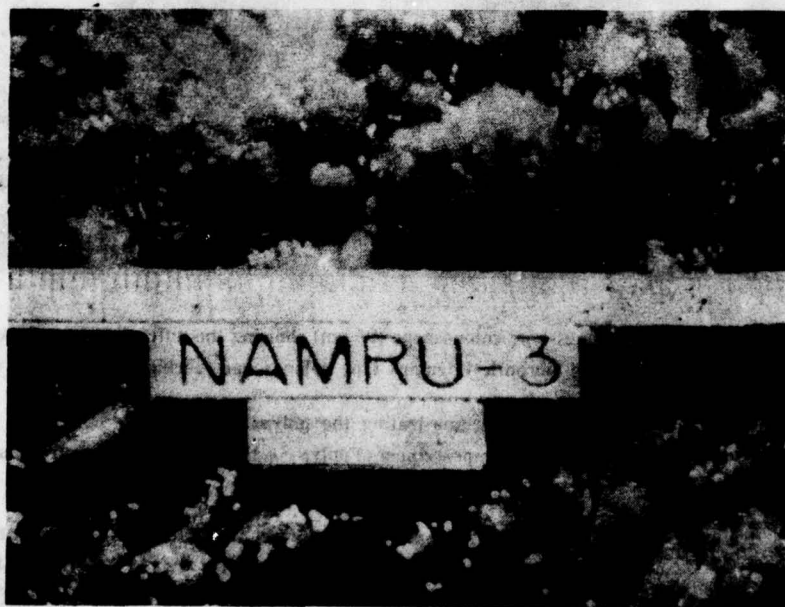


Fig. 1. — Post mortem autopsy of colon opened to show multiple polyps protruding in lumen

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The purpose of the first part of this investigation was to evaluate by direct visual observation, through a colonoscope (Fig. 2), the effect of medical treatment in 15 patients with schistosomal polyposis. The colonoscope consists of an eye view-

ing apparatus attached to a lens at its other end by several fiberoptic bundles grouped together inside this tube with transverse lining to indicate depth. Pictures or movies can be taken (see Figs. 6-12).



Fig. 2.—View of fiberoptic Olympus type colonoscope (95 cm) showing the different parts of the instrument.

Fig. 3.—X-ray of the 165 cm long fiberoptic Olympus type colonoscope reaching from rectum to ascending colon.

Fig. 4.—Barium enema with air contrast demonstrating the polyps.

Fig. 5.—(a) Post-treatment X-ray showing improvement of polyp condition seen on the pre-treatment X-ray(b).

Initial clinical evaluation is shown in Table 1.

Passage of blood in stool and diarrhea were the most common symptoms and all patients had a prior history of schistoso-

miasis. Physical examination revealed hepatomegaly in 47% of patients and splenomegaly in 33%. Some suffered from ascites and/or oedema in the lower limbs, scrotum and abdominal wall skin.

TABLE 1.—Initial evaluation of 15 patients.

Symptoms:	Hematochezia	100% of patients
	Diarrhea	10 bm/ day*
	Recurrent schistosomiasis	100% of patients
Physical:	Hepatomegaly	47% of patients
	Splenomegaly Ascites and oedema	33% of patients
Laboratory studies:		
Liver function:	Alkaline phosphatase	3.8 ± 0.5 U/ml (0.8—2.3)
Serum proteins:	Albumin	2.6 ± 0.3 (3.5—5.2 g%)
Anemia:	Hemoglobin	9.3 ± 0.76 (14—15 g)
Parasitology:	Stools	Positive for <i>S. mansoni</i> 100% of patients
	Miscellaneous parasites	Positive — 40% of patients

(*) bm = bowel movement

Laboratory studies demonstrated hyper-alkaline-phosphatasemia, hypoalbuminemia, and anemia (Table 1).

Stool and urine examinations revealed mixed *Schistosoma mansoni*-*haematobium* infection in 11 of 15 patients, while three patients had pure *mansoni* infection and one had a pure *haematobium* infection. Other parasites, such as hookworm, *Ascaris*, or *Hymenolepis nana* were found in 40% of patients.

Multiple polyps were seen from the rectum to the transverse colon on barium enema, with the greatest concentration of polyps found in the sigmoid colon, specifically at the rectosigmoid junction (Fig. 4).

Sigmoidoscopy and colonoscopy revealed colonic polyposis in all patients (Figs. 6-12).

Twelve patients had more than 25 polyps while three patients had less than 20.



Fig. 6.—Demonstrates many polyps in one area of the colon.

Fig. 7.—Shows polyps covered by friable and bleeding mucous membrane.

Fig. 8.—An example of multiple polyposis seen in one of the patients studied.

The polyps were generally friable and covered by a white exudate; they were associated with a bleeding and unhealthy mucous membrane (Fig. 7).

All patients were subjected to colonoscopic biopsy for making permanent sections and crush preparations.

All patients were found to have viable eggs on biopsy prior to treatment. Embryo viability was most easily determined by two methods: (1) direct microscopic examination of the crushed biopsy specimen and (2) by hatching procedures using pond water.

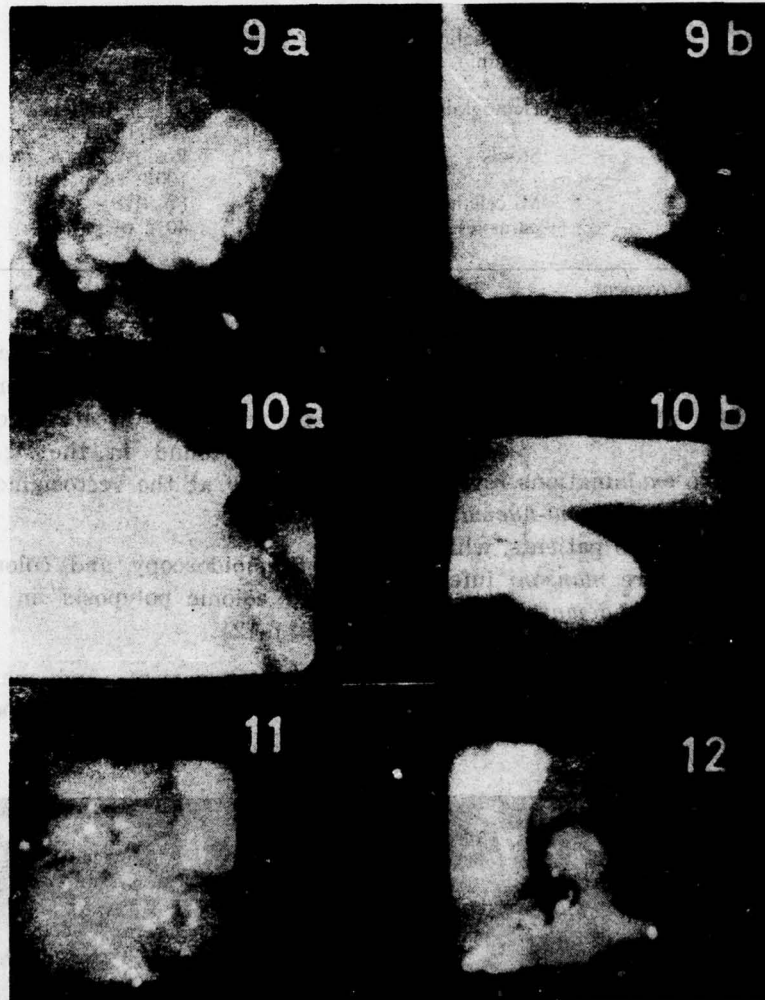


Fig. 9.—(a) Pre-treatment endoscopic picture and (b) 6 months post-treatment picture demonstrating improvement.

Fig. 10.—Post-treatment endoscopic pictures (a) six months and (b) 12 months after treatment showing further improvement (stumps only remaining).

Fig. 11.—Example of cauliflower-like multiple polyposis, five years post-treatment.

Fig. 12.—Biopsy-taking, from polyp, by biopsy forceps introduced inside the fiberoptic colonoscope.

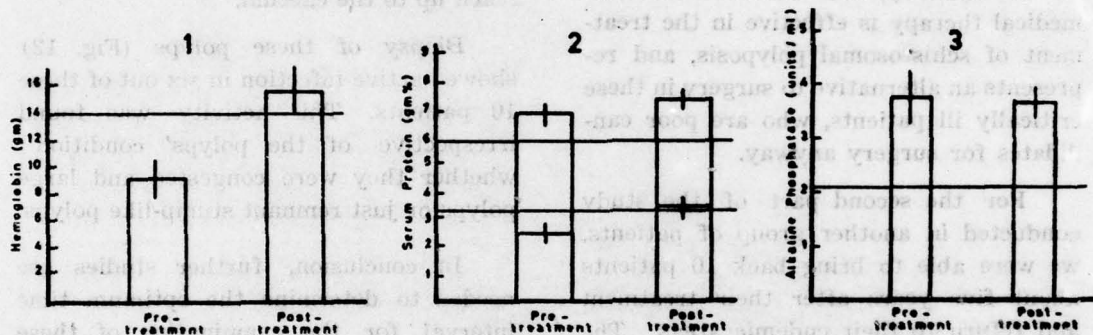
Treatment consisted of routine medical supportive therapy such as the administration of fluids, of antibiotics such as tetracycline and of anti-inflammatory drugs as cortisone. Ferrous sulphate was also given for correction of anemia. Niridazole (Ambilhar) at a dose of 25 mg/kg per day for 10 days, instead of the conventional six days, was the specific anti-bilharzial therapy used.

Side effects were nausea, vomiting, mental disorientation and psychosis — fortunately all reversible. Two patients

experienced drug reactions that required discontinuing therapy; both patients recovered without complication after the drug was stopped.

Follow-up studies were performed at 3, 6, and 12 months. Clinical improvement was recognized by three months and by six months there was no diarrhea nor passage of blood in stool.

Physical examination revealed the persistence of the previously noted hepatosplenomegaly and a mean 6-month weight gain of 10 pounds.



Graphs 1-3. — 1. Correction of anemia after treatment. 2. Return of serum albumin to normal level after therapy. 3. Alkaline phosphatase level has remained unchanged after treatment.

Graphs 1, 2 and 3 show the pre- and post-treatment laboratory investigations; both the anemia and hypoalbuminemia were corrected 12 months after treatment. The transaminases and bilirubin levels remained normal and there was no significant change in post-treatment alkaline phosphatase.

Stools and urines were negative for active, viable eggs in all patients after three months, and a barium enema revealed gradual resolution of the polyps as demonstrated in Fig. 5a,b, which shows the pre-treatment condition (a) and the post-treatment condition (b). As can be seen in this figure, there is nearly com-

plete resolution of the extensive pre-treatment polyposis.

The rate of polyp resolution was variable but all patients showed marked improvement when observed by barium enema and colonoscopy within 12 months.

On the endoscopy picture (Fig. 9a,b), Fig. b, made 6 months after treatment, was taken at the same depth of insertion as the pre-treatment picture (9a) and the largest polyp within ± 5 cm of this point was chosen for presentation. It is seen that the necrotic pre-treatment polyps are no longer present and in addition to the marked reduction in polyp size, all 6-month post-treatment biopsies were negative for viable eggs.

Figs. 10a,b show the 6 and 12-month colonoscopy in the same patient and reveal that after 12 months only small polypoid stumps remained.

The polypoid stumps seen in the above figures are covered by normal colonic mucosa which may or may not contain dead schistosome eggs. Biopsies were negative for viable eggs in all patients three months after treatment and a review of permanent sections of colonic mucosal biopsies revealed no significant histologic abnormalities.

In summary, these data indicate that medical therapy is effective in the treatment of schistosomal polyposis, and represents an alternative to surgery in these critically ill patients, who are poor candidates for surgery anyway.

For the second part of the study conducted in another group of patients, we were able to bring back 10 patients about five years after their treatment and return to their endemic areas. The colonoscopy used in the long term follow-

up is the more sophisticated Olympus type (165 cm in length) with which we can reach almost up to the caecum, as seen in Fig. 3.

The clinical condition, symptomatology and general physical examination of these 10 patients was fairly good.

Preliminary results show that the mean hemoglobin content was 12.8 g and mean serum albumin 3.3 g. However, the polyp condition varied from stumps to cauliflower growths (Fig. 11) that may reach up to the caecum.

Biopsy of these polyps (Fig. 12) showed active infection in six out of these 10 patients. This activity was found irrespective of the polyps' condition; whether they were congested and large polyps or just remnant stump-like polyps.

In conclusion, further studies are needed to determine the optimum time interval for the examination of these polyp patients.

THE MODE OF ACTION OF ANTIMONY ON *SCHISTOSOMA MANSONI*

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Antimonials inhibit the glycolysis of *Schistosoma mansoni* *in vitro* (Bueding, 1950) and the enzyme phosphofructokinase (PFK) (Mansour and Bueding, 1954) and alter the levels of sugar phosphates in worms from antimony treated mammals (Bueding and Fisher, 1966; Fisher et al., 1966). It has therefore been concluded that antimony is lethal to schistosomes through its inhibition of PFK (Bueding, 1959, 1969, 1972; Bueding and Fisher, 1966, 1969). As immature *S. mansoni* are more resistant to antimony therapy than adults (Standen, 1955a; Stohler and Frey, 1963) it should be possible to show biochemical differences between immature and adult worms that will account for the differential response to antimony.

Materials and Methods

White mice (Hough or Alderley Park strains) were infected by paddling or the abdominal ring technique with *S. mansoni* cercariae (Wellcome strain), 180 cercariae per mouse being used for adult infections and 2,000 cercariae per mouse for recovery of three week old worms. Worms

were collected by perfusion through the dorsal aorta with ice cold citrate saline.

Antimony taken up by the worms 2 hr after a single intraperitoneal dose of KSb tartrate (25 mg/kg) was assayed by the method of Howie et al. (1965). The methods of Bueding and Fisher (1966) were used to determine the effects of KSb tartrate on PFK of worm extracts and on the levels of hexose phosphates in worms treated *in vivo*. The rates of glycolysis *in vitro* were determined by measuring lactate production after incubation of worms for 1½ hr under air in Tyrode or Tyrode plus 10⁻⁴M KSb tartrate.

Results

Oral and intraperitoneal dosing of antimony to infected mice confirmed that immature worms are more resistant to chemotherapy than adults (Table 1). However the antimony levels in three week old worms 2 hr after dosing ($0.349 \pm \text{S.E.M. } 0.03 \mu\text{g/mg dry weight}$) was not significantly different from that found in adults ($0.44 \pm \text{S.E.M. } 0.09 \mu\text{g/mg dry weight}$).

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TABLE 1. The activity of oral and intraperitoneal antimony against *Schistosoma mansoni*. Oral dosing 200mg/kg \times 5, intraperitoneal 25mg/kg \times 5.

Route of administration	Dosed on days	No. of worms found \pm S.E.M.	% cure
oral	—	44 \pm 5.5	—
„	21—25	25.5 \pm 2.9	42
„	42—46	1.6 \pm 0.8	96
intraperitoneal	—	117.6 \pm 9.2	—
„	21—25	140.8 \pm 8.8	0
„	42—46	72.5 \pm 7.7	38

In six groups of adult worms 90 min. incubation in 1×10^{-4} M KSb tartrate reduced lactate production by 48% compared to 64% in three week old worms. These results were remarkably close to those of the effect of KSb tartrate on PFK. 3×10^{-5} M KSb tartrate inhibited

PFK from extracts of immature worms by 65.5% compared to 46.5% in adult extracts. Measurement of worm hexose-phosphate levels 2 hr after dosing animals with KSb tartrate (25 mg/kg) showed similar inhibition of PFK in both stages of worms (Table 2).

TABLE 2. The effect of KSb tartrate (25mg/kg) 2 hr after dosing mice on the levels of hexosephosphates in *Schistosoma mansoni*. (3 week old worms μ g/1000 worms, adults μ g/g wet wt of worms).

Experiment	Treatment	Stage	G6P+F6P (μ g)	Ratio treated: untreated
1a	control KSb tartrate	3 week old	0.34 0.84	2.5 : 1
1b	control KSb tartrate	„	0.50 0.99	2.0 : 1
1c	control KSb tartrate	„	0.32 0.69	2.2 : 1
2	control KSb tartrate	adults	80 168	2.1 : 1
3 Bueding and Fisher (1966)	(a) control	„	57	1.3 : 1
	KSb tartrate	„	73	
	(b) control	„	40	2.5 : 1
	KSb tartrate	„	100	
	(c) control	„	65	1.0 : 1
	KSb tartrate	„	65	

Discussion

Our results have failed to show differences in the effect of antimony on schistosomes that can account for the differences in response of adult and three week old worms to antimony therapy. Thus the levels of antimony taken up by worms *in vivo* 2 hr after dosing were not significantly different, and *in vitro* immature worms appeared more sensitive to KSb tartrate than adults as measured both by the effect on the enzyme PFK and on the rates of glycolysis. Further, the results of inhibition of PFK *in vivo* as measured by changes in hexose phosphate levels failed to show differences between immature and adult worms. While therefore there is no doubt that KSb tartrate inhibits PFK of *S. mansoni* both *in vitro* and *in vivo*, (as reported by Bueding and co-workers), the failure to find a difference at the level of PFK between the two stages calls into doubt whether antimony kills worms by inhibiting this enzyme.

However, two parameters require further investigation before this conclusion can be validated. It is possible that the kinetics of antimony retention in immature and adult worms may be dif-

ferent ; over a longer period than 2 hours the immature worms may eliminate antimony faster than adults. It is also possible that the adult worm infection may be so altering the kinetics of excretion of antimony by the mouse that the worms in a mature infection are effectively exposed for a longer period to the drug than would be immature worms. Experiments to study these possibilities are in progress.

If antimony does not kill schistosomes by direct inhibition of PFK it may be asked how it acts. Two possibilities at present can be offered. Standen (1955b) has suggested that one of the main actions of a schistosomicide is to enable the host to recognise the presence of foreign protein which can then be attacked and destroyed. Antimony could possibly do this directly or indirectly. Alternatively specific accumulation in certain cells may interfere with vital functions of the worm, and Erasmus (1975) has shown accumulation of antimony by the vitelline cells in female worms.

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CLINICAL EVALUATION ON THE USE OF PENICILLAMINE AS A CHELATING AGENT WITH TARTAR EMETIC IN THE TREATMENT OF SCHISTOSOMIASIS

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Many attempts have recently been made to study the influence of penicillamine on the antibilharzial effect of tartar emetic, T.E. ; (potassium antimonyl tartrate) as well as on its toxicological manifestations in experimental animals. Penicillamine was found to diminish the acute toxicity (Khayyal et al., 1967), electrocardiographic (ECG) changes (Girgis et al., 1970) and fluctuations in liver functions (Khayyal et al., 1973) induced by tartar emetic in various animals. On the other hand, penicillamine did not markedly affect the antischistosomal action of the antimonial, when given in a dose-ratio of 1:2 to tartar emetic. Higher ratios of Penicillamine were found to inhibit the curative action of the drug (Khayyal et al., 1973).

The present study was conducted on a limited clinical scale to investigate whether penicillamine would exert the same beneficial effect on man, as it did in experimental animals.

Materials and Methods

The study was conducted on 50 male schistosomiasis patients ; their ages ranged from 15-30 years ; 40 of them were suffering from the urinary form and the rest (10 patients) from both the urinary and intestinal form of the disease. All were suffering from their infection,

with complaints of dysuria, haematuria, tenesmus and/or diarrhea. All patients were passing schistosome ova. Every patient was given tartar emetic intravenously every other day in a dose of 1/2 grain/15 kg body weight for a total of 12 injections. The penicillamine or placebo capsules were given in a dose of 150 mg per person three times daily, starting 2 days before, and ending 2 days after, the tartar emetic course, according to a preset code, unknown to the authors.

The laboratory and clinical tests carried out before treatment included a 24 hr urine and stool egg count on 2 successive days, total and differential blood count, estimations of the serum glutamic oxalacetic transaminase (SGOT) serum glutamic pyruvic transaminase (SGPT) and lactic acid dehydrogenase (LDH) enzyme and isoenzyme pattern, as well as electrocardiogram (ECG) recording.

Upon starting treatment, the patients were observed daily for side reactions. Electrocardiographic tracings were performed one hour after each injection of the antimonial during treatment, then weekly for 8 weeks after cessation of therapy. Blood counts and liver function tests (SGOT, and LDH) were carried out weekly during treatment and during the follow-up period of two months. The stool and urine egg counts were performed im-

mediately after completing therapy, then once monthly for two months.

The common side effects of anti-monial therapy, namely, vomiting, cough and malaise were graded according to their intensity into moderate and severe. Moderate symptoms involved coughing for a very short period during or immediately after the injection, severe symptoms involved coughing for several times accompanied by nausea, vomiting, and generalized weakness.

Results

Twenty five patients received T.E. and placebo and 25 T.E. and penicillamine. The two groups were comparable as regards age and intensity of infection; 5 patients from each group had a mixed infection and the remaining 20 had *S. haematobium* only; the mean 24 hr ova counts were comparable, ranging from

2,000-50,000 ova per 24 hr stool or urine collection.

All patients receiving T.E. + penicillamine were able to complete the full course, whereas in the other group receiving T.E. + placebo, therapy had to be discontinued in 4 patients (16%). These patients developed fever with a marked increase in eosinophilic count, generalized weakness and muscle pain. The symptoms appeared after the 5th injection in two of them, and after the 6th injection in the other two. They slowly regained their health after stopping the injections. In the remaining 21 patients, the reactions were severe in 14 (60%) moderate in 4 (19%) while only 3 patients (14%) had no reactions. The incidence of adverse reactions in the other group was lower, 10 (40%) showing a severe reaction, 1 (4%) a moderate reaction while 14 (56%) showed no side effects. These results are summarized in Table 1.

TABLE 1.— The incidence of side-effects in bilharzial patients treated with tartar emetic alone or in combination with penicillamine.

Severity of Side Effects	Tartar Emetic Alone	Tartar Emetic + Penicillamine
None	3 (12%)	14 (56%)
Moderate	4 (16%)	1 (4%)
Severe	18* (72%)	10 (40%)
Total number of patients	25	25

(*) Including 4 cases in which severe side effects necessitated discontinuation of the drug.

Alterations in the ECG pattern usually became apparent after the 5th dose. The changes were in the form of inversion in the T-wave and depression of the ST segment. The commonest leads affected were L_3 , V_3 and V_4 .

In the T.E. + placebo treated group, 6 (28%) patients had no changes, 6 (28%) patients showed changes in 2-4 leads, and 9 (44%) showed changes in more than 4 leads. However, in the penicillamine — tartar emetic treated group, 10 patients

(40%) showed no changes, 11 (44%) showed changes in 2-4 leads and only 4 (16%) showed changes in more than

4 leads (Table 2). All the changes observed were temporary and disappeared during the follow-up period.

TABLE 2. Incidence of ECG changes

	Tartar emetic	Tartar emetic + Penicillamine
None	28%	40%
2-4 Leads	28%	44%
> 4 Leads	44%	16%

A two-fold increase or more in SGOT and SGPT was observed in 4 patients receiving T.E. alone and in only one patient receiving penicillamine as adjuvant. Similarly the total LDH increased in 8 patients receiving T.E. alone and in two patients receiving the combined therapy. This increase was accompanied by an increase in the percentage of the heart LDH.

There was no direct correlation between the severity of side reactions, ECG changes and biochemical abnormalities on one hand, and the age, weight, intensity and nature of the infection on the other.

The cure rates as measured by the absence of ova in the urine and stools 8 weeks post-treatment were comparable in both groups. Three patients from each group were still passing eggs, denoting failure of treatment.

Discussion and Conclusion

Our clinical findings confirm the experimental data previously obtained, i.e., that when penicillamine is administered in conjunction with Tartar Emetic therapy it markedly reduces the toxic side reactions of the latter without affecting its therapeutic activity (Khayyal et al., 1967).

Ron Pedrique & Ercoli (1971) using penicillamine-potassium or sodium antimony tartrate complexes found that they were very well tolerated, and their toxicity was lower than that of T.E. alone. In this way the dose of antimony may be increased without undue toxicity and better cure rates can be achieved.

The major complaints occurring during antimonial therapy viz. cough, vomiting and malaise, which are usually responsible for discontinuation of treatment, were minimal in the patients receiving penicillamine.

Many theories have been put forward to explain the ECG changes, however the exact cause still remains unknown. There was no correlation between the severity of the side reactions and the ECG changes. Thus it would seem advisable that ECG tracings be performed on all patients receiving T.E. as a routine procedure.

The rise in transaminase levels, mainly in patients under antimonial therapy alone, is in accordance with reports from other authors (Pantrizel et al., 1963; Asshauer & Mohr, 1966; Coutinho & Barreto, 1969). Such changes were hardly observed in the group of patients receiving penicillamine as adjuvant (one patient in 25).

The mechanism of toxicity of antimonials to the host has not yet been fully elucidated. Most of the evidence available suggests that antimony combines intracellularly with SH group containing enzymes, leading to inactivation of vital systems and processes in the cell. Accordingly, the adjuvant use of penicillamine

would tend to chelate the antimonial, leaving the body enzymes free (Khayyal et al., 1973). This would help to explain the beneficial effect of penicillamine demonstrated in this work, i.e. that of reducing the incidence and severity of side effects encountered with antimonial therapy.

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- The rate of excretion of the drug and its metabolites in the urine and stools was not significantly different between the two groups. Three patients from each group were still passing eggs, denoting failure of treatment.
- Discussion and Conclusion**
- The clinical findings confirm the experimental data previously obtained, i.e. that when penicillamine is administered in conjunction with tartar emetic, it markedly reduces the toxic side effects of the latter without affecting its therapeutic activity (Khayyal et al., 1973).

A SELECTIVE APPROACH TO THE CONTROL OF SCHISTOSOMIASIS

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Developing nations are beset with so many health problems that it sometimes becomes difficult to choose priorities wisely. It is not unusual to find that a particular infection or disease has to such an extent impressed itself upon health administrators or physicians in general, that other more urgent problems are neglected. This may be due to the romantic or scientific appeal offered by the disease or to public pressures for action, but is more commonly to be found in conditions which are easily expressed by prevalence figures, freely available through the use of some simple and inexpensive survey technique (stool examination, immunological procedure, etc.). Man likes to have his facts clear-cut; how very much easier it is to say that 5% of the Brazilians have a positive complement fixation test for Chagas' disease than to evaluate the importance of malnutrition, believed to be a contributory cause for death in up to 60% of the mortality in infancy and childhood. It is obviously very much simpler to perform a stool examination or an intradermal test than to define the real impact of protein-calorie deficiency in the pathology of a tropical country.

I'm not trying to be facetious when I say that the appeal of schistosomiasis to many authorities is to be rooted upon the ease with which it can be formulated by numbers. Another feature to be recognized, and which it has in common with other parasitic diseases, is that therapy

is so effective in the individual case that «eradication» seems just around the corner, a view which has been actively fostered by the drug companies.

I have always been in full disagreement with this sort of oversimplification, and my opinions are often held to be somewhat heretical, if not outright pessimistic. Nevertheless, many years of field work in the hyperendemic areas of Brazil have led to the conclusion that schistosomiasis mansoni is very rarely a cause of death, and that even chronic illness is not very common. While splenomegaly, a very sensitive index of hyperendemic conditions, can be found in up to 10% of a population, only some 15% of these actually develop hematemesis (a very ominous sign) and some 2 or 3% present liver failure. Furthermore many tropical infections are multifactorial, and can truly be labeled «social diseases»: frequent exposure to schistosome cercariae should not be viewed only as a consequence of the presence of infected snails within a focus, but as a corollary to insufficient sanitation, lack of adequate water supply, bad working conditions and total absence of health education, in short, the syndrome of underdevelopment.

It thus seems unrealistic to believe that the eradication of infectious diseases can ever outpace the growth rate of the economy of a nation, or proceed at a faster rate than the improvement of living conditions.

Still, the medical profession has a duty to perform. It is often necessary to blind oneself to the long-range prospects and overall panorama, and in a very pragmatic and direct fashion proceed to the attempt of preventing and alleviating human disease. Notwithstanding my somewhat dogmatic views and my rejection of the demagoguery which involves much of Public Health planning in some countries, I accept the challenge of schistosomiasis, but would like to be selective about it. I would propose the selection, among those millions who are merely infected by *Schistosoma mansoni*, of the thousands who are ill because of fluke disease, concentrating our efforts upon this group only, or better still, I would like to be able to recognize those individuals who are fated to develop severe schistosomiasis, and prevent such an outcome.

But, when is schistosomiasis mansoni a disease, rather than a very common infection?

A tropical disease should be recognizable by the presence of signs and symptoms specific to such a single agent, and unrelated to concomitant factors such as malnutrition, chronic fatigue and stress, or other infection. This is often a difficult order to fill. In *S. mansoni* infections (to which I will confine my comments) these specific features include portal hypertension (betrayed by splenomegaly and its major complication: hematemesis), liver failure and pulmonary shunting or hypertension. It is true that endocrinological deficiencies have been recognized among the effects of severe schistosomiasis, though it is not always easy to attribute this specifically to fluke infection.

I'm not at all happy about schistosomiasis, and would like to be able to

contribute something to its control. But this is a hopeless task if we persist in clouding the real issue, and go on spreading ourselves thinly over a vast country with the modest funds available for practical work. «Eradication» is a word to be banned from our thoughts unless sweeping changes can be effected in the social conditions of the underdeveloped areas. Until such a day arrives a very selective approach has to be adopted.

Selection of a Geographical Area

The distribution of schistosomiasis mansoni in Brazil is very heterogeneous, comprising areas with an overall prevalence close to 90%, as well as circumscribed foci, some of which were discovered in recent years, where infection is limited to that minority of the population working under unfavourable conditions, or to a small number of schoolchildren fortuitously infected in a creek or water-hole. One would be tempted to dismiss these foci as unimportant, as well as those other areas exhibiting only modest prevalence figures.

But opposition to these views among official circles is great. It is reasoned that schistosomiasis is in a process of expansion within the country, owing to internal migration from the endemic areas to the developing south, as well as to new irrigation projects, and that these new and still unimportant foci will eventually turn into major centers for the disease, so that preventive measures become urgent. Thus the state of São Paulo, the most affluent of the country, is allocating to schistosomiasis funds and manpower many times higher, on a *per capita* basis, than are devoted to the hyperendemic areas in other states.

I believe that these policies should be re-examined. Not only is it surmisable

that the postulated spread of schistosomiasis throughout Brazil is to a large extent a reflection of increasing awareness of this parasite, and the large numbers of surveys that have been carried out in recent years in states hitherto believed to be exempt, but it appears likely that ecological conditions in the cool south will not be favourable to the establishment of hyperendemic conditions, so that *S. mansoni* will remain confined to a few, sporadic foci. Social conditions are vastly better than in the other states, and the population in contact with unprotected water sources is limited.

To me it seems logical, therefore, to concentrate all efforts towards the control of schistosomiasis to those areas where prevalence in the general population is high.

Sub-selection within an Area

The model area here considered is a composite of six towns in northeastern Brazil (states of Pernambuco, Sergipe and Alagoas) with 7,500 inhabitants; the overall prevalence of schistosomiasis *mansoni* is 62% on the basis of stool examination, and 92% if the intradermal test was used. It would, thus, qualify as a hyperendemic area and be chosen as a likely candidate for a control project, whether «mass treatment» is adopted, or snail control is used as the more efficient tactic. The area embraced by snail control would be very large while, if chemotherapy should be used, some 5,000 individuals would have to be treated. Cost of this project would be high, and administrative difficulties enormous. Furthermore, in the event of an unavoidable drug accident at the beginning of the work, the whole project would be doomed: not only is it likely that the population would refuse further cooperation, but the staff itself would adopt an overly cautious atti-

tude, and hesitate about pursuing the same tactics.

Cannot the procedure be simplified?

Table 1, also based upon concrete figures, indicates wide differences in the patterns of schistosomiasis between the four zones of our model town. Zone A comprises the center of town, which is adequately supplied with running water. It is thus easy to understand why prevalence is not as high as elsewhere, that egg counts for *S. mansoni* are low and that few cases of severe schistosomiasis are found in the population. Zone B comprises the streets located close to a major river which, as is usual in northeastern Brazil, does not offer favourable conditions for the transmission of schistosomiasis, owing to rapid flow and lack of vegetation. Thus the problem within the town seems to be limited to zones C and D.

TABLE 1. Schistosomiasis in the various parts of the model town.

Zone	Stools positive for <i>S. mansoni</i>	Median egg counts	Population with splenomegaly
	%		%
A	55	85	2
B	65	110	3
C	87	325	13
D	80	295	11

If a selective approach to the control of schistosomiasis is adopted, which of the parameters in Table 1 should be taken as an indicator of the severity of endemic conditions?

While prevalence figures have been found to be roughly parallel to egg counts and clinical data when the various areas

of the same town are compared, these figures may be misleading in the comparison between different localities, since prevalence and severity may be unrelated under these conditions. Furthermore, these data are extraordinarily dependent upon the sensitivity of the diagnostic test employed in a survey.

Much more useful for the selection of priorities are average or median egg counts within the different populations, as well as the spleen index. The former is specially suited for children (since splenomegaly develops only in the 10-15 years bracket), the latter cannot be used in adults, because egg counts decline very fast at the end of adolescence, whatever their original level.

Clustering within Families

Selectiveness in action against schistosomiasis can be carried one step further.

In every area I have studied over all these years a remarkable clustering of severe schistosomiasis (high counts as well as splenomegaly) has been observed within familial groups. This finding, which initially led to the hypothesis (very quickly abandoned) that portal hypertension in schistosomiasis might be genetically determined, was actually the first hint that worm burdens might be related to clinical severity, an idea later confirmed through longitudinal studies in groups of children.

Table 2 reproduces some of these data.

TABLE 2. Family clustering of parameters in schistosomiasis

Locality studied	Human material (age)	No. of individuals	Parameter chosen	Prevalence in general population	Families*		
					No. of Families	No. of individuals	Prevalence of parameter
Gameleira (Pernambuco)	Over 8	304	Splenomegaly	14%	46	166	73%
Gameleira (Pernambuco)	All ages	333	Egg counts over 500/g	20%	34	187	33%
Jabuticatubas (Minas Gerais)	All ages	192	Egg counts over 250/g	10%	6	26	58%
Cajueiro (Alagoas)	8 — 14	575	Splenomegaly	8%	43	194	17%
Cajueiro (Alagoas)	8 — 14	575	Egg counts over 500/g	28%	41	187	60%
Santana do Mundaú (Alagoas)	6 — 12	186	Egg counts over 500/g	31%	19	54	61%
Santana do Mundaú (Alagoas)	6 — 12	126	Splenomegaly	13%	9	21	62%

* At least one member of which exhibits the parameter indicated.

Clustering is obviously not a characteristic of families as such, but of populations exposed to similar epidemiological conditions. Once a family with severe schistosomiasis is located, a survey of the neighborhood will usually reveal many other similar cases. The foci responsible for hyperendemicity are often peridomiliary, and consist of small creeks, drainage ditches or even temporary pools formed during the rainy season. These are of such modest dimensions that they are frequently missed by the field teams, but examination of the snails shows an infection rate many times higher than in other areas of the town.

The body of data hitherto amassed indicates that an area endemic for schistosomiasis may be broken down into subunits, intelligent guess-work often allowing the selection of a few hazardous areas, on which control work should be concentrated. The procedure which I will outline has been identified as an «index-case cluster method» by a WHO epidemiologist (which came as a pleasant surprise).

Index-case Cluster Method

The index case may either be an individual with a high egg count (500 eggs/g is the threshold suggested), or a case of splenomegaly. These can be identified at the start of a project whether through random investigations, a survey of school-children or even by inquiries among local physicians, pharmacists or community leaders concerning individuals suffering from «water belly» (ascites) or past episodes of hematemesis.

Starting with these index-cases, one can proceed to a study of the family groups, the neighborhood and, finally, to the identification of the foci responsible for transmission.

All my investigations in schistosomiasis have taken advantage of the extraordinary stability of human population in most areas of northeastern Brazil, a characteristic which also favours implementation of the control measures outlined above. Families live for decades in the same place and expose themselves to foci which vary very little from year to year, a phenomenon which explains why similar clinical patterns of schistosomiasis develop in individuals whose age may differ by 30 or more years.

But population stability is not met with in all the hyperendemic areas of Brazil, which limits the general usefulness of the index-case cluster method.

Selective Chemotherapy

The strategy described above will have some appeal for the practical physician, who is accustomed to reasoning in terms of limited objectives, and quite contented with the perspective of identifying and treating a small group at risk of severe schistosomiasis. Those trained in Public Health, however, will look at my proposal with mixed feelings.

Public Health aims at achieving significant and long-lasting improvements in health conditions, and would like to adopt control schemes on a larger scale than my more individualistic approach to a small number of hazardous foci of schistosomiasis. And then index-case tracing demands dedicated attention by a group of highly motivated personnel, and such man-power is always in short supply.

I believe, however, that the following suggestions will find a better reception on the part of the health strategist.

Table 3 gives an estimate of egg excretion for *S. mansoni* in different age groups, based upon data collected in a small Brazilian town.

TABLE 3. Number of eggs excreted by infected individuals in Gameleira, Brazil.

Age-group (years)	% of total population	Number in population	Median egg count (per gram)	Number of eggs excreted daily (in thousands)
0 — 4	16.3	864	0	0
5 — 9	13.6	721	75	13.519
10 — 14	12.4	657	284	46.154
15 — 19	10.3	546	310	42.315
20 — 29	17.2	894	143	31.960
30 — 39	12.0	636	171	27.189
40 — 49	8.1	429	70	7.507
50 — 79	9.1	553	70	9.681
			Total	178.325

Traditional «mass treatment» would involve chemotherapy in practically the entire population of this area, since prevalence at all ages above infancy is close to 90%. Our scheme, however, would limit treatment to the 10-19 age-group, which comprises 22.7% of the population, but is responsible for half of the schistosome eggs passed daily. On a *per capita* basis, therefore, chemotherapy would be 2.2

times more effective than indiscriminate mass treatment. It would also prove to be more useful, since in this group the more serious consequences of schistosomiasis can still be reduced or entirely prevented.

But the concept of selectiveness does not have to stop here, as is illustrated by Table 4.

TABLE 4. Distribution of egg counts in 100 individuals 10-19 years old in Gameleira

Class (eggs/g)	Class midpoint	Number of individuals	Number of eggs per day per 100 individuals
Negatives	—	17	0
0 — 49	25	4	25. 000
50 — 99	75	14	262. 500
100 — 149	125	2	62. 500
150 — 199	175	3	131. 250
200 — 299	250	11	743. 750
300 — 399	350	6	525. 000
400 — 499	450	1	112. 500
500 — 999	750	24	4.500. 000
Over 1000	1,150	14	4.025. 000

If chemotherapy is limited to those with egg counts over 500/g, one would again obtain dividends out of proportion to the investment made. That group comprises 38% of the population but is responsible for 78% of the eggs eliminated: It is also the group running a higher risk of developing hepato-splenic schistosomiasis.

A combination of the two criteria, i.e., selection of those with egg counts over 500, and limitation of treatment to the 10-19 age-group, would result in treatment of only 8.6% of the general population yet the number of eggs released would be reduced by 39%, yielding a multiplication factor of 4.5 (admitting 100% effectiveness of the drug). Will this suffice?

Whether selective treatment by itself can turn the tide of transmission of schistosomiasis remains to be seen. Since at present socio-economic factors operating in northeastern Brazil are apparently accompanied by a slow and gradual reduction in the rate of transmission, selectiveness in chemotherapy might be sufficient to achieve that state which Macdonald called the «break-point».

It would not even be necessary to perform stool examination of 23% of the population, since severe schistosomiasis and high egg counts are concentrated in certain foci, which can easily be identified by a preliminary survey.

The method described possesses an additional advantage. Since the hazards of unpredictable accidents have to be accepted in schistosomiasis, whatever the drug used, their number will obviously decrease if mass treatment is abandoned in favour of a more selective procedure. In addition, since patients with high egg counts form a group at risk of developing portal hypertension (or have already

developed it), chemotherapy is the only medical option open to the individual, and one can find sufficient moral justification for exposing him to the lesser risk of a therapeutic accident. This will not be the case in indiscriminate mass chemotherapy, a procedure which by definition encompasses a large majority of individuals who will always remain asymptomatic.

I have confined my remarks to chemotherapy, for it appears to be the control method of choice in most situations. There is no reason, however, why this procedure cannot be combined with snail control, which also will become more practical if certain foci are selected in preference to others. These can be identified very accurately by their proximity to areas where egg counts in the population are high, and the clinical patterns of schistosomiasis severe.

Concluding Remarks

The story is widely known:

A famous mountaineer was once asked why he took all this trouble to climb a particular peak. He hesitated for just one moment, then answered: «why... because it's there».

This quotation has a meaning: sometimes I can't escape the impression that schistosomiasis, too, claims so much attention on the part of health authorities just because it's there; an analysis of its clinical implications, the real impact upon the morbidity of populations, is usually forgotten. Yet, once critical evaluation of the morbidity due to *S. mansoni* is undertaken, it will become apparent that in most areas the problem is very much secondary to other Public Health issues. It will also lead to the recognition of a few areas in which the disease is hyper-endemic, with some effects upon human health. It will then become clear that

limited control of schistosomiasis is entirely feasible, if realistic goals are drawn up.

For some time I have flirted with the idea of devising a set of criteria for the evaluation of endemic conditions in schistosomiasis mansoni. These criteria would permit the comparison of different areas and the establishment of priorities, as well as judgement concerning progress in the control of the infection.

The following proposals are open to criticism and should be seen as preliminary suggestions, to be discussed thoroughly before adoption :

Stage A : No new cases of splenomegaly in the area (provided that malaria and Kala-Azar are not endemic).

Stage B : Prevalence of schistosomiasis mansoni in the 0-4 year group not higher than 30%.

Stage C : Prevalence in the 0-4 year group not higher than 10%.

Stage D : Overall prevalence not higher than 10%.

Once stage A is reached it can be admitted that hyperendemic conditions have ceased, and that the inhabitants do not acquire high worm burdens any more.

Stages B and C reflect reduced rates of transmission. In the endemic areas of Brazil exposure to the foci starts in the first two years of life, and changes in prevalence in young children will be a sensitive and early index of the transmission of schistosomiasis. I concede that stages A and B may to some extent overlap.

I hope this suggestion can be discussed in this meeting.

I'm aware that many sweeping statements made in my presentation are unsupported by the text, and reference must be made to the various papers published by the author from 1962 to the present date.

**ASSESSMENT OF THE EFFECTS OF SOME CHEMOTHERAPEUTIC AGENTS
ON THE HAEMOSTATIC MECHANISM IN SCHISTOSOMAL
HEPATIC FIBROSIS**

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Hepatic schistosomiasis is frequently associated with bleeding manifestations. Multiple defects in the haemostatic mechanisms have been described. Hypoproteinaemia refractory to vitamin K (Ghanem et al., 1970), hypofibrinogenaemia and reduced thromboplastic activity (Zaher et al., 1971) were previously stressed. Enhanced fibrinolytic activity together with increased levels of fibrinogen degradation products were also demonstrated (Tawfik et al., 1974). Thrombocytopenia too and defective platelet functions were elucidated (Zaher et al., 1971).

The underlying aetiological mechanisms have not been ascertained. Enhancement of fibrinolytic activity, both primary and secondary, is related to an increase in tissue activators and to defective clearance mechanisms (Tawfik et al., 1974). It has been suggested that consumption coagulopathy triggered by tissue thromboplastic material stemming either from associated infection or of renal origin was the operating factor (Verstraete et al., 1971).

Hepatocellular impairment may lead to the defective synthesis of coagulation factors, to activation of fibrinolysis or to an increase in circulating anticoagulants.

In order to investigate the pathogenesis of the coagulation defect, Johanson (1964) observed the effect of heparin on a patient with advanced liver cirrhosis. He reported a rise in platelet number and in the level of several coagulation components, which denotes that hypercoagulability plays a role in the pathogenesis of bleeding in liver disease.

The aim of the present work is to assess the effect of the administration of various coagulation inhibitors (heparin, trasylol, epsilon amino-caproic acid) on blood coagulability, fibrinolytic activity, and platelet count and function in schistosomal hepatic fibrosis (SHF) patients with bleeding attacks.

Material and Methods

The present study was made on 28 male SHF patients aged from 24 to 47 years. They were suffering from attacks of haematemesis. They comprised the following groups :

1. Eight patients who received 500 mg of intravenous heparin in divided doses every 4 hr for two days.
2. Ten cases to whom 50,000 kallikrein inactivator units of trasylol were given every 2 hr for two days by continuous drip infusion.

* Deceased, 1977.

3. Ten SHF patients with primary fibrinolysis to whom 30 g of intravenous epsilon amino-caproic acid (EACA), Capramol, Choay Laboratories (Paris) were administered over three days. These patients showed an increase in the fibrinogen degradation products level above $40 \mu\text{g/ml}$ in their sera; they had normal platelet counts and increased fibrinolytic activity.

Prior to and immediately after the trials coagulation studies were done which included determination of the bleeding time, coagulation time, prothrombin activity (Bigg & Macfarlane, 1962), a partial thromboplastin generation test (Marjolis, 1958), plasma fibrinogen (Varley, 1962), euglobulin lysis time (von Kaulla, 1963), Adenosine diphosphate (ADP) induced platelet aggregation (Cook & Symmons, 1966), platelet adhesiveness (Caspary, 1964), platelet count and the slide latex test for fibrinogen degradation products (Allington, 1970).

Twelve normal healthy persons were used as controls, the same tests being

simultaneously made on them (values are included in Table 1).

To evaluate changes in hepatocellular integrity, routine liver function tests were made, including those for total serum proteins and their fractionation, for serum transaminases, alkaline phosphatases and pseudocholine esterases, thymol turbidity, zinc sulphate turbidity and serum bilirubin.

During the trial no adjuvant haemostatic agents, including blood transfusion, were given to the patients.

Results

Following heparin therapy, stoppage of haematemesis was achieved in two cases and amelioration was observed in another case. There occurred a significant elevation (Table 1) of plasma fibrinogen (37.1%), of euglobulin lysis time (30.5%), of platelet adhesiveness (24.8%) together with an increase in the platelet count (29.4%) and in platelet aggregation (30.1%). In six cases fibrinogen degradation products (FDP) showed a level below $10 \mu\text{g/ml}$.

TABLE 1. — Effect of intravenous heparin on the haemostatic mechanism in schistosomal hepatic fibrosis patients (Mean \pm S.D.)

Test	Control	Before heparin	After heparin
Bleeding time	2' 48" \pm 0.32	3' 10" \pm 0.45	3' 28" \pm 0.62
Coagulation time	3' 25" \pm 1.2	6' 35" \pm 1.1	6' 48" \pm 1.2
Prothrombin %	95.4 \pm 10.3	58.3 \pm 7.2	60.4 \pm 9.8
P.T.G.T.*	61.3" \pm 9.4	74.2" \pm 8.3	69.0" \pm 7.2
Fibrinogen mg%	288 \pm 48	205 \pm 42	286 \pm 53
Euglobulin lysis time	233' \pm 31.6	144' \pm 28.6	188' \pm 33.4
Platelet count \times 1000/ml.	388 \pm 86.0	174 \pm 28.0	255 \pm 32
Platelet adhesiveness %	22.3 \pm 5.2	16.7 \pm 2.3	20.8 \pm 3.5
Platelet aggregation	21.6' \pm 3.5	28.1' \pm 5.7	29.3' \pm 4.6
F.D.P.			
Below $10 \mu\text{g/ml}$	12 cases	2 cases	6 cases
Between $10-40 \mu\text{g/ml}$	—	4 cases	2 cases
Above $40 \mu\text{g/ml}$	—	2 cases	—

(*) P.T.G.T. + Partial thromboplastin generation test.

In 30% of patients marked improvement was seen in respect to their bleeding tendency after trasylol. This was associated with a remarkable diminution (Table 2) of fibrinolytic activity (35.3%)

together with an increase of thromboplastic (21.8%) and prothrombin (19.2%) activities. A reduction of FDP to normal levels was noted in 40% of cases.

TABLE 2. Effect of intravenous trasylol on the haemostatic mechanism in schistosomal hepatic fibrosis patients (Mean \pm S.D.)

Test	Before trasylol	After trasylol
Bleeding time	3' 15" \pm 0.61	3' 20" \pm 0.42
Coagulation time	3' 42" \pm 1.3	4' 10" \pm 1.6
Prothrombin %	62.1 \pm 8.1	73 \pm 9.2
P.T.G.T.*	74.2" \pm 9.3	58" \pm 8.2
Fibrinogen mg%	195.3 \pm 38.2	282 \pm 42.0
Euglobulin lysis time	164.0' \pm 29.3	222' \pm 49.0
Platelet count \times 1000/ml	182.0 \pm 42.3	190 \pm 39.3
Platelet adhesiveness %	15.6 \pm 2.4	16.9 \pm 3.2
Platelet aggregation	37.0' \pm 4.4	35.0' \pm 3.8
F.D.P.		
Below 10 μ g/ml	3 cases	7 cases
Between 10-40 μ g/ml	4 cases	2 cases
Above 40 μ g/ml	3 cases	1 case

(*) P.T.G.T. = Partial thromboplastin generation test.

After intravenous EACA, marked amelioration as regards bleeding was noted in half of the patients (Table 3). Fibrinolytic activity showed a significant

reduction (49.6%). A marked rise of plasma fibrinogen (30.7%) and platelet count (34.5%) occurred. The FDP showed a level below 10 μ g/ml in eight cases.

TABLE 3. Effect of intravenous epsilon amino-caproic acid (EACA) on the haemostatic mechanism in schistosomal hepatic fibrosis (Mean \pm S.D.)

Test	Before EACA	After EACA
Bleeding time	3' 25" \pm 0.48	3' 32" \pm 0.65
Coagulation time	6' 25" \pm 1.2	6' 45" \pm 1.8
Prothrombin %	62.4 \pm 7.8	65.5 \pm 9.2
P.T.G.T.*	75.6" \pm 8.5	68.3" \pm 7.2
Fibrinogen mg%	195.0 \pm 38.4	255.0 \pm 32.6
Euglobulin lysis time	135.0' \pm 31.6	202.0' \pm 42.0
Platelet count \times 1000/ml	165.0 \pm 23.0	222.0 \pm 28.0
Platelet adhesiveness %	16.5 \pm 2.2	18.3 \pm 3.1
Platelet aggregation	37.6' \pm 4.9	32.4' \pm 4.3
F.D.P.:		
Below 10 μ g/ml	4 cases	8 cases
Between 10-40 μ g/ml	2 cases	1 case
Above 40 μ g/ml	4 cases	1 case

(*) P.T.G.T. = Partial thromboplastin generation test.

It must be pointed out that administration of these drugs in the mentioned doses was not accompanied by aggravation of the bleeding tendency or by other superadded complications. Investigation of various liver functions revealed almost no deterioration of the defects in hepatocellular integrity already present.

Discussion

Administration of trasylol and EACA, which possess an inhibitory effect on fibrinolysis, resulted in diminution of bleeding and in enhanced fibrinolytic activity. At the same time we noted an associated increase in the plasma fibrinogen level and a decreased incidence of cases with elevated FDP. This clearly points to the important role played by primary enhancement of fibrinolysis in the genesis of the bleeding tendency in hepatic schistosomal involvement. Similarly Grossi & Monera (1964) demonstrated that EACA led to control of fibrinolysis and bleeding during portocaval shunts in Laennec's cirrhosis.

EACA by inhibiting plasminogen and plasmin may lead to such effect on fibrinolytic activity. Astrup et al. (1960) suggested that in cirrhosis there exist tissue activators not due to liver damage but due to vascularised connective tissue rich in fibrinolytic activity.

In addition to these previously mentioned effects, trasylol injection led to increased thromboplastic activity in SHF. This may be brought about by the tendency of trasylol to inhibit the preliminary phase of blood coagulation. Since it is a proteinase inhibitor, the operating mechanisms might encompass a possible concomitant effect on tissue lysosomal

enzymes and on tissue proteinases with a resulting decreased activity of released tissue thromboplastins.

Trial of heparin was associated with elevation of platelet count, of plasma fibrinogen and improvement of platelet function. These results agree with those of Johanson (1964) in Laennec's cirrhosis. This strongly indicates the presence of an underlying consumption defect. Products of hepatic necrosis gaining access to circulation may initiate and perpetuate intravascular clotting. The consumption defect is probably of renal origin. Perhaps a disseminated intravascular thrombosis associated with precipitation of fibrin in the glomeruli might cause or complicate renal diseases (Verstraete et al., 1971). A diminution of heparin probably resulted in the interruption of such a mechanism by secondary changes in the different haemostatic parameters.

The present study throws light on the possible application of anticoagulant therapy as an adjuvant line of treatment, in the management of haemorrhagic manifestations in schistosomiasis.

Summary

The effects of the administration of trasylol, epsilon amino-caproic acid and heparin on the haemostatic mechanism were tested in 28 schistosomal hepatic fibrosis patients with haematemesis. Amelioration of the bleeding tendency was noted. Reduction of fibrinolytic activity and increase in fibrinogen level accompanied trasylol and epsilon amino-caproic acid trials. In addition parenteral heparin injection was associated with improvement in platelet count and function.

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GLOBAL STATUS OF HYCANTHONE : A REVIEW

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Since its commercial introduction late in 1969, hycanthonne methanesulfonate (hycanthonne mesylate; Etrenol®) has been used for the treatment of approximately 1.2 million patients infected with *Schistosoma haematobium* or *S. mansoni*. Records indicate that between November 1969 and October 1975 the number of vials distributed for clinical use was 1,293,713. Of this number 532,857 went to Brazil and the Caribbean ; 419,814 went to the Middle East ; 250,711 went to Southern Africa (So. Africa, Rhodesia, Zambia, Malawi and Mozambique) ; 69,409 went to East Africa ; 20,187 went to Central and West Africa ; and 735 went to satisfy requests in European centers. On the basis of enquiry and visits to various clinics and hospitals, it was conservatively estimated that 20% of vials remained as inventory, and 15% of the remainder treated two children each. Inasmuch as many clinics used the vials of hycanthonne promptly, the number treated must have been in excess of the calculated 1,190,216. Teratogenic, mutagenic or carcinogenic effects in humans treated with hycanthonne have not been reported.

The only serious adverse reaction which has been associated with the clinical use of hycanthonne is an acute hepatic necrosis. Fortunately this reaction has been relatively rare and the incidence can be reduced by adherence to directions for use and care in selection of patients. A

total of 70 fatal reactions have been reported or disclosed by investigation of rumours. Many of them occurred in the early days of use of the drug and under conditions in Africa where medical supervision was minimal. Analysis of the 70 reports indicates that in 12 instances the primary factor was other disease during the course of which hycanthonne was administered (e.g., typhoid fever, peritonitis, ruptured varices, cerebral atrophy, terminal kala azar, terminal kwashiorkor, etc.). The problem of evaluating the reported adverse reactions is illustrated by the death of one patient who was admitted to hospital with diagnosis of severe viral hepatitis and received hycanthonne a few days later, whereas another jaundiced patient was subjected to two doses of hycanthonne separated by a course of niridazole during the febrile course of typical hepatitis — and survived.

In 42 other instances the role of hycanthonne was highly questionable because of extenuating circumstances such as serious violations of the guide lines for treatment, e.g. : treatment on the sole basis of history of hematuria without pre-treatment physical or laboratory examination ; in-hospital administration of overdose of hycanthonne to malnourished child four days after major surgery under general anesthesia ; unrecognized post-necrotic hepatic cirrhosis ; existing severe anemia and malnutrition, etc.

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In six instances procedure had been correct and death was due to acute post-treatment hepatic necrosis without apparent pre-disposing factors. In ten instances the information was insufficient for evaluation but the reactions have been accepted as drug induced. In other words 54 (77%) can be classified as avoidable while there is no recorded basis for exclusion of 16 (23%). It should be noted that most of the fatal reactions occurred during the first two years of use of hycanthone whereas the greatest consumption has been in the subsequent three years. There has been considerable variation in geographic distribution of reactions. This variation reflects the experience of early or late extensive use of hycanthone. After exclusions, the ratio of reactions to number treated is : in Southern Africa 1:25,628 ; in Brazil 1:163,409 ; in the Middle East 1:386,228 ; in East Africa 1:63,857 and in Central and West Africa, where use has been smallest, 1:18,572. For total use of hycanthone, the ratio of deaths to number treated is 1:74,388. It is noteworthy that 468,647 vials went to 17 countries from which no fatal reaction has been reported. It should also be noted that, irrespective of region, fatalities have been associated with outpatient clinics largely dependent on paramedical staff. No deaths have occurred during large scale control treatment campaigns where there has been competent screening of those to be treated.

The efficacy of hycanthone against both *S. haematobium* and *S. mansoni* has been well established ; it should be noted that clinical investigators who base their «cures» on absence of *viable ova* report cure rates of 80 to 100%, whereas those who do not distinguish between dead and *viable ova* report «cure» rates ranging from 48 to 70%, attributable to continuing excretion of residual dead ova for

weeks or months after parasitological cure has been attained.

There has been continued agitation against the use of hycanthone which has centered about extrapolative claims of potential tetratogenic, mutagenic and carcinogenic effects of hycanthone.

Hycanthone is undoubtedly capable of inducing certain types of «mutagenic» changes in certain mutant strains of microorganisms and neoplastic tissue culture cells under static *in vitro* conditions which differ significantly from the dynamic processes in intact higher animals. Submammalian test systems for mutagenicity of drugs have not been accepted as predictive of mutagenic potential for humans (WHO, 1971).

The various experimental studies of possible mutagenic effects of hycanthone in intact mammals will be discussed more authoritatively by Dr. W.L. Russell during this symposium. Suffice it to say that such studies have been essentially non-significant with respect to genetic hazard of hycanthone for humans.

Inasmuch as a major component of the fear of potential carcinogenic effect of hycanthone was the result of extrapolation from *in vitro* submammalian test systems for mutagenicity, the accumulated evidence that hycanthone is not mutagenic when administered to mammals under conditions of clinical use (*i.e.*, dose level and route of administration) tends to allay fear of carcinogenicity. However, this degree of relief does not dispel the need for properly designed and controlled life-span tests for carcinogenicity carried out in suitable laboratory animals (*e.g.*, mice, rats, hamsters).

The only published claim of evidence that hycanthone has been carcinogenic in animals is the report by Haese, Smith & Bueding (1973). Their data had previously been submitted to and reviewed by a WHO Consultant Group which met in Geneva June 26-29, 1972 (see WHO Reports on Schistosomocidal Drugs. II, 1972). On page 95 of this report: «Preliminary information by Haese and Bueding (personal communication) in *S. mansoni* infected mice led to a significantly higher incidence of gross masses and hyperplastic changes in the liver than in nontreated animals. Hepatomas were found in eight mice (4.7 per cent) treated with hycanthone but not in untreated mice or infected mice treated with a nitrovinylfuran (SQ 18506)». The expert opinion was «Excessive weight should not be placed on this observation in view of the difficulties in assessing the significance of mouse hepatomas in carcinogenicity studies in general, as well as in instances where there is pre-existing pathology».

More important, Yarinsky et al. (1974), in an 18 month life-span study in mice, found that neoplasias were not more frequent in hycanthone treated mice (infected and noninfected) than in either infected or noninfected controls. In their publication Haese, Smith and Bueding (1973) conceded that hycanthone was not carcinogenic in noninfected mice but «concluded that the hepatic hyperplasia, induced by the deposition of schistosome eggs in the liver and enhanced by hycanthone, is a predisposing factor for a hepatocarcinogenic effect of the drug». This interpretation is refuted by the data of Yarinsky et al. (1974). Furthermore, Sieber et al. (1974), p. 227, state after reference to Haese et al. (1973): «However, data from our laboratory (Adamson, unpublished observation) as well as recent report by Yarinsky et al. (1974) indicate

that hycanthone is not carcinogenic in mice». (The Adamson study, from the National Cancer Institute, is to be published soon). A life-span carcinogenicity test of hycanthone (IM) being conducted at the Eppeley Institute is to be concluded in July 1976; it was still negative at 12 months.

Teratogenicity does not present a major problem in the clinical use of hycanthone. In the laboratory, when administered to pregnant mice (SC) and rabbits (IM) at dose levels 10-25 times the clinical use dose of 2-3 mg/kg hycanthone is embryotoxic or teratogenic when administered at a critical period of gestation (Sieber et al., 1974). Although treatment of schistosomiasis in pregnant women has not been recommended it is known that hycanthone has been administered inadvertently in early pregnancy, and at later stages when the physician felt that the clinical condition of the patient justified the risk. In one project where such cases are being monitored, there have been no abnormalities among 90 offspring who were exposed to hycanthone *in utero*. It is significant that there has not been a single report of a teratogenic or mutagenic effect in relation to approximately 1.2 million persons treated to-date.

Prospective use of hycanthone. The consultant group convened by WHO in Geneva in June 1972 reviewed available schistosomicides with respect to possible usefulness in schistosomiasis control campaigns. After consideration of all available evidence concerning efficacy and safety, it was concluded that hycanthone and niridazole were suitable for use in control campaigns. Questions concerning potential mutagenicity and carcinogenicity were left open pending ongoing studies, but it was concluded that the available evidence would not justify stop-

ping the use of either substance for the treatment of schistosomiasis. The significance of subsequent reports of experimental mutagenicity and carcinogenicity will be appraised during this symposium. Significant mutagenicity or carcinogenicity of hycanthone has not yet been demonstrated.

Aguirre et al. (1972) reported that in a two-year period following a single dose (3.0 mg/kg) of hycanthone administered to essentially all infected persons in a community, and in the absence of other control measures, the incidence of *S. mansoni* dropped sharply and progressively in several communities in Brazil, e.g., from 13.6% to 0.66%, 20.3% to 1.12% and 83.5% to 19.8%. The data strongly suggest that transmission was arrested or greatly reduced. Also Baquir (1974, 1975) has reported good results in the control of *S. haematobium* in Iraq by use of hycanthone in areas where mollusciciding had also been applied with varying effectiveness, but the most conclusive evidence of the potential use of hycanthone as a control measure is coming from the island of St. Lucia and is being summarized by Dr. Jordan and his colleagues in this symposium. In preliminary studies, Cook and Jordan (1974a,b) found that the dose of hycanthone could be reduced as low as 1.5 mg/kg and still reduce the excretion of *S. mansoni* ova by 97-98%. There was a concomitant reduction of the principal side effect — vomiting. There was some loss of efficacy in terms of «cures» but for control purposes the reduced excretion of ova and increas-

ed acceptability are more important. In Brazil dosages of 2.0 and 2.5 mg/kg have shown improved tolerance and only slight reduction of curative action. We understand that Cook, Jordan and Bartholomew (1975) have apparently arrested transmission of *S. mansoni* in the Marquis Valley of St. Lucia by use of 2.5 mg/kg for the treatment of all suitable infected patients in the valley. Christie and Upatham (1975) recently reported «...after treatment of infected humans, in March 1974, no infected field snails have been found to the present». (October 1974). They also reported that it had not been possible to infect laboratory raised monitor *Biomphalaria glabrata* exposed as part of the surveillance of the Marquis Valley during the same period.

It is now clear that chemotherapy, alone or in conjunction with snail control, offers an essential tool in campaigns to control schistosomiasis. At present, hycanthone is the only available schistosomicide which is highly effective against both *S. haematobium* and *S. mansoni* and extensive experience indicates that with proper medical supervision and screening it is sufficiently safe for use in control campaigns. Teratogenicity in humans has not been reported, it is not mutagenic in mammals and convincing evidence of carcinogenicity in animals has not yet been reported in multiple high dose trials. Larger scale trials in endemic areas appear to be justified and there is still much to be learned about the optimum organization and use of trained teams for the most effective mass chemotherapy.

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INVESTIGATIONS FOR TRANSMITTED GENETIC EFFECTS OF HYCANTHONE IN MICE*

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The original concern over a possible genetic hazard from the use of hycanthone arose from results of a microbial test (Hartman et al., 1971). Officials in the World Health Organization were, on the one hand, disturbed by the possible risk, and, on the other hand, worried that a useful drug might be banned solely on the basis of a bacterial test which might turn out not to be predictive of the effect of the drug in mammals. At this point, our laboratory was approached by WHO for assistance in trying to resolve the problem. Our Mammalian Genetics Section of the Biology Division of Oak Ridge National Laboratory has accumulated the most extensive set of data available on possible *transmitted* genetic effects of hycanthone in mammals. For example, our group has conducted the largest dominant lethal study performed on this drug or perhaps any drug. This has involved repeated as well as single doses, two entirely different strains of mice and, what is not usually done in other laboratories, a dominant lethal test on treated females as well as males. Our laboratory is the only one that has subjected hycanthone to the X-chromosome-loss test and tests for transmitted deficiencies and gene mutations in a mammal.

When there has been any indication of a possible genetic effect we have pursued that work further and checked the possibility with more rigorous methods.

It would be inappropriate to present to this audience the technical details of our genetic tests and the masses of data produced from them. However, it may be helpful to give a brief history of the succession of experiments performed by our group over the past five years, and a summary of the results obtained. This should give some basis for appraising the validity of the conclusions reached. The references can be consulted for more detailed information.

Our first test was a dominant lethal experiment on male mice injected intraperitoneally with 150 mg/kg of hycanthone (50 times the therapeutic dose). There was no effect. When the experiment was repeated on a second strain of mice, there was again no effect. Repeated daily doses of hycanthone were then injected into male mice over five days for a total dose of 208 times the therapeutic dose. This also gave no dominant lethal effect. All of these experiments were run on a large scale (Generoso et al., 1972).

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Having shown no evidence of transmitted chromosomal damage, as measured by the dominant-lethal test, we turned to the possibility of being able to detect the induction of gene mutations by hycanthone. Here we used the specific-locus test developed in our laboratory, originally for measuring the genetic effects of radiation, but subsequently used in chemical mutagenesis investigations. In addition to scoring for gene mutations, this method also detects small chromosomal deficiencies.

Our preliminary results from the specific-locus test were reported in Cairo, in December 1971, at the Afro-Asian Symposium on Schistosomiasis. We have now scored for mutations in a total of 16,196 offspring from males injected with 50 times the therapeutic dose of hycanthone, and not a single mutation has been observed (Russell and Kelly, 1972; Russell, 1975).

Perhaps the most meaningful question to ask about this result, so far as human risk is concerned, is whether the sample size is large enough to exclude the possibility of a mutation rate of a magnitude that might be considered unacceptable. In other words, if a particular low mutation rate is chosen as an upper limit for an acceptable risk in the use of an antischistosomal drug, was the specific-locus experiment big enough to detect a mutation rate that low? The level of detectability attained in our experiment can be expressed in the following way. If we take the upper 95% confidence limit of the observed zero number of mutations, which is 3.3, subtract the known spontaneous mutation frequency from this and divide by 50, on the assumption, presumably conservative, that the therapeutic dose of 3 mg/kg will give no more than 1/50th of the mutation rate produced by 150 mg/kg, then we arrive

at an induced mutation rate which is only 6% of the spontaneous rate. Thus, the sample size in our experiment was large enough to show that, if hycanthone is capable of inducing any gene mutations or transmitted deficiencies in male mouse germ cells, the frequency from a dose of 3 mg/kg is unlikely to be more than a small fraction of the spontaneous rate. Even the upper 95% confidence limit of the observed zero mutation frequency is below the level of a 10% increase over the spontaneous mutation rate, a level which was suggested to WHO as an acceptable risk for an efficient antischistosomal drug.

Having found no evidence of any mutagenic effect of hycanthone in treated male mice, we decided to extend the testing to females. Here we found, in the first experiments, some indication of damage transmitted to the offspring. In later work there was clear-cut proof of this. Before this statement is taken out of context and allowed to induce the kind of panic that arose over the finding of a mutagenic effect of hycanthone in *Salmonella*, it should be emphasized that when the results are used to estimate the human risk, this turns out to be very small indeed, if not zero, from the therapeutic dose. In fact, the study on females provides a model demonstration of the great importance of exploring a positive effect in depth, both qualitatively and quantitatively. Recommendations based on an isolated positive finding, and without consideration of dose level, can be misleading.

The first effect noted in the offspring of females injected with hycanthone was a reduction in litter size (Generoso et al., 1972). The effect was curiously limited to the progeny conceived in the first week following treatment. Because of this limitation, it was at first thought that the

effect was probably not a true genetic one, but possibly a consequence of toxicity in the mothers. Since the litter-size reduction could have resulted solely from killing of some of the mature or maturing oocytes, a dominant-lethal test was undertaken in order to settle this question (Generoso et al., 1972). The results showed that at least the major part of the effect was not due to killing of oocytes, but to death of embryos. However, even though the distribution of deaths relative to age of embryos was typical of that seen in dominant-lethal experiments, the possibility that the embryo lethality might be a result of toxicity in the mothers, rather than a genetic effect, was still not rigorously excluded. We therefore turned to the X-chromosome-loss method to see if this would reveal positive identification of genetic damage in the offspring.

With this method, developed in our laboratory, treated females are mated to males carrying the sex-linked gene «greasy» (Gs). The offspring are scored for presumed Gs/0 females, i.e. females lacking one X-chromosome, which are checked by breeding tests and chromosome counts in cultured ear tissue. Chromosome counts of the mothers of these females are also made, to exclude any cases where the parent is already XO.

The results have been presented elsewhere (Russell et al., 1975). The frequency of X-chromosome losses in offspring from first-week matings of females injected with 150 mg/kg of hycanthone is significantly above the control value. As with the litter-size results, the effect is limited to the first week: the offspring from treated females mated in later weeks show no increase in X-chromosome loss frequency over that in the controls.

Having obtained a clear-cut induction of X-chromosome loss, as shown in off-

spring conceived in the first week after intraperitoneal injection of females with 150 mg/kg of hycanthone, we decided to explore the dose-effect relationship. Although the sample is still small, the frequency at 75 mg/kg already shows a drop significantly below that expected on a linear interpolation between 150 mg/kg and zero dose ($P = 0.01$, relative likelihood test) (Russell et al., 1975). The induced frequency (i.e. with control subtracted) at 75 mg/kg, instead of being 1/2 of that at 150 mg/kg, is only 1/10. The effect on litter size also showed a drop below linearity. The practical conclusion seems clear, that linear interpolation between 150 mg/kg and zero dose would have grossly overestimated the effect of the therapeutic dose of 3 mg/kg. This may also be true for linear interpolation between zero dose and 75 mg/kg, which is still 25 times the therapeutic dose.

In all the experiments reported so far, we had used intraperitoneal injection, and it was suggested that the potent effect in the female, and its curious limitation to conceptions occurring in the first week after treatment, might be due to the fact that the ovary is directly exposed to peritoneal fluid. Furthermore, the most mature oocytes are near the surface of the ovary. A small experiment measuring effect on litter size was run in which intraperitoneal injection was compared with three other routes of administration: intramuscular and subcutaneous injection, and gavage. A clear-cut reduction in litter size was observed only with the intraperitoneal injection (Hunsicker and Russell, 1975). Since intramuscular injection is the route used in hycanthone therapy, the results on litter size indicated the importance of comparing intramuscular and intraperitoneal injection for X-chromosome loss induc-

tion. Preliminary data now obtained from this comparison, which will be reported in detail elsewhere, show that intramuscular injection is less than one-quarter as effective.

Using the above results, we can make an estimate of what the risk of X-chromosome loss might be in the offspring of treated females. If we calculate the effect expected from the therapeutic dose, assuming linearity between the 75 mg/kg dose and zero, adjust for the reduced response with intramuscular injection, and allow for the fact that very few of the total conceptions in the population of treated females are likely to occur in the first week after treatment, then we arrive at a risk of approximately one X-chromosome loss per 40 million conceptions. Even this low frequency is presumably an overestimate, because we have assumed a linear response with dose. There may well be a threshold dose response, and no effect at all at the therapeutic level.

Most human X-chromosome losses terminate as early abortions. Other chromosome losses do too, and are, therefore, not a very serious hazard. If, at worst, the X-chromosome loss induction seen is only the top of an iceberg of other chromosomal types of damage, it could still be said that even a total damage 100-fold greater than that actually observed would surely rate as an acceptable risk in the use of an effective antischistosomal drug.

Adding together all the results on transmitted genetic effects in mammals obtained by our laboratory and others (summarized in Russell, 1975), there appears to be no genetic basis for changing the WHO conclusion of 1971, reaffirmed in 1972, that there are «no reasons sufficient to justify a recommendation that the use of hycanthone for the treatment

of schistosomiasis should cease». (WHO, 1971, 1972).

Many factors obviously have to be weighed in the choice of a drug for chemotherapy of schistosomiasis, but if a selection were to be based solely on mutagenic risk, one might take the following point into consideration. On the one hand, there are several old and new drugs of which none has been adequately tested for possible mutagenic effects. On the other hand, there is hycanthone, which has now been subjected to more mutagenic testing than any other drug on or off the market. The tests used include the most definitive ones, namely investigation for transmitted chromosomal aberrations and gene mutations in mammals. Most of these have shown no effect at all even at very high multiples of the therapeutic dose. One test has shown an effect at high doses. However, when that result is used to calculate the expected genetic effect at the therapeutic dose, the estimate of risk ranges from zero to, at most, a tiny fraction of the naturally occurring, spontaneous frequency of mutational events.

Thus, there would appear to be little difficulty in making the choice on genetic grounds. Rather than use a genetically untested or inadequately tested drug, it would seem preferable to use the one that has been extensively tested and that has so far, in mammalian tests, proved to be either genetically innocuous or very close to it.

We sincerely hope the results of our investigations will be of some assistance in reaching wise decisions on the chemotherapy of schistosomiasis. Since this is not a disease with which we are cursed in the United States, we have been proud that the decision to pursue our genetic work was generously funded by the United

States in a spirit of assistance to Egypt and other countries in tropical regions.

When we started our work we, along with WHO, were afraid, on the basis of the microbial tests, that hycanthone might prove to be a serious genetic

hazard. We are, of course, delighted that it has not turned out that way at all; that, instead, our extensive investigations have not revealed any genetic risk near the level that would suggest banning this drug from its valuable role in the chemotherapy of schistosomiasis.

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SCREENING OF TWO NEW SYNTHETIC ORGANIC TRIVALENT ANTIMONIALS FOR POTENTIAL ANTISCHISTOSOMAL ACTIVITIES IN MICE

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ABSTRACT

Two new synthetic trivalent antimonials with fairly high molecular weight, i.e. antimonyl 7 formyl quinoline (A.F.Q.) and antimonyl pyrimidine (A.P.R.M.), in which the antimony (Sb) portion of the molecule is complexed with aromatic bases via phenolic oxygen linkages, have been subjected to an array of screening tests for possible therapeutic efficacy against *Schistosoma mansoni* infected mice. Parallel experiments were made with Tartar Emetic (T.E.) as a reference standard. Besides, acute toxicity studies of the three antimonial congeners have been conducted in adult normal albino mice to determine their relative toxicolo-

gical potencies and margin of safety. The results of the oogram method devised by Pellegrino and Katz (1969) revealed that though T.E. significantly exceeded the other two test compounds in antischistosomal activity in the lower range of dosage (up to ED_{50} values), yet in large doses coinciding with ED_{84} , the two novel antimonials approached and even exceeded (in the case of A.F.Q.) the reference standard in potency. Judged by the calculated ratios of LD_{10}/ED_{84} for each compound, A.F.Q. and A.P.R.M. proved much safer than T.E., surpassing the margin of safety of the latter agent twice and 7 times respectively.

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SOME NEW TOXICOLOGICAL PARAMETERS OF NIRIDAZOLE

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ABSTRACT

In this study, which was performed on rats, the investigation was directed towards the detection of the effect of niridazole on the basal body temperature and blood oxygen. The drug was given to normal albino rats of both sexes in doses equivalent to double and 5x the therapeutic level. The changes in rectal temperature and blood oxygen together with the percentage of hemoglobin in the blood were measured 3 and 5 hr after administration. The same parameters were estimated after

repeating the oral administration for 5 days at the stated dose levels. Niridazole was found to possess a hypoxemic effect which is directly proportional to the dose level and period of administration. A compensatory increase in hemoglobin was noticed. A primary insignificant rise in temperature was recorded, but hypothermia was evident after 24 hours and most magnified after 5 days of administration. This hypothermic effect was more marked at the larger dose level.

ENDOSCOPIC DIAGNOSIS IN SCHISTOSOMIASIS

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ABSTRACT

Endoscopic diagnosis of schistosomiasis may be useful in detecting not only the presence of the disease (histological or cytological diagnosis of ova), but also in the diagnosis and management of complications.

Oesophago-gastro-duodenoscopy (OGD) has been discussed in relation to the early diagnosis of oesophago-gastric varices and in the identification of the exact site of upper alimentary haemorrhage.

This will be discussed in relation to experience of over 5,000 examination in the Department of Medicine at Bristol.

In addition, fibre-optic colonoscopy — both its technique, feasibility and practical application has been discussed with particular relation to the diagnosis of inflammatory large bowel disease and inflammatory pseudo polyps. This subject is discussed with reference to 800 colonoscopies performed in our Department.

HISTOLOGIC AND RADIOLOGIC IMPROVEMENT OF BILHARZIAL COLONIC POLYPOSIS FOLLOWING TREATMENT WITH NIRIDAZOLE

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THIRD PLENARY SESSION

**EVALUATION OF MOLLUSCICIDAL CONTROL OF SCHISTOSOMIASIS
IN THE MIDDLE EAST**

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It is a great honour to welcome you to this plenary session of the conference, hoping that our deliberations will reveal recent advances and effective guidance in the subject and practice of molluscicidal control of schistosomiasis. This problem has been so far most baffling, particularly in certain areas, where there is an extensive irrigation system with a widely spread drainage network in which water is continuously flowing from one system to the other throughout the year. Egypt is such an example; the land is never dry throughout the year. The Nile valley and delta have been described as a large water-bottle with a long neck. The Nile has been flowing from South to North for ages providing water for all living organisms, and continuously repopulating its valley with snails. The immensity of this problem has almost hindered the success of mollusciciding as a control measure against schistosomiasis in countries with extensive perennial irrigation. In such countries mollusciciding proved to be an expensive procedure requiring repeated blanket applications interspersed by frequent focal treatments, because snails repopulate canals after a comparatively short period, usually 2-3 months. Water channels in hot climates may become schistosomiasis-infective approximately 6 weeks after reinfestation with

fresh eggs of snails, if eggs only drift inside the channels.

The problem is less serious in other countries in which the system of irrigation consists of more or less separated units, each of which is irrigated by means of a central canal whose branches terminate in dead ends, and which are subjected to dryness in summer. The intakes of the central canals originate from a large feeder canal. This type of irrigation system is practically void of drains. Snail control can be economically achieved by the application of molluscicide, as it can be adjusted to the biology and ecology of the snail host at the appropriate time in order to interrupt transmission, and can be followed up by focal treatment of reinfected portions of canals (usually the terminal parts). This irrigation type is found in Lebanon, Iran, Syria and Iraq. I confine my present statement to countries in the Eastern Mediterranean Region, where I have visited several countries, conducting initial surveys and planning pilot schistosomiasis-control projects in some.

In addition to the two types of irrigation system mentioned above, there is a third type, the so-called oasis-type of irrigation, such as occurs in Saudi Arabia, Libya and Tunisia. The Arab Yemen

* Deceased, 1977.

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Republic can be included to a certain extent. In these countries, interruption of transmission can be easily achieved by elimination of snail intermediate hosts. In the meantime prevalence of the disease can be reduced by mass-treatment. In Egypt in Dakhla Oasis, schistosomiasis disappeared completely as a result of the eradication of *Bulinus truncatus* and the treatment of the infected population.

This is more or less the general situation in the Eastern Mediterranean Region; but in order to throw light on the mollusciciding results, I limit myself to brief accounts on the situation in each country, and leave specific statistical data to be delivered by the experts of the various projects who are participating in this conference.

The projects established by the governments and assisted by the World Health Organization (WHO) through its Eastern Mediterranean Regional Office (EMRO), were pilot projects, the main objectives of which were collecting epidemiological and malacological base-line data, applying the appropriate control measures and conducting the training of national staff. The evaluations were carried out by the WHO advisers of the projects and in certain instances by independent specialised WHO short term consultants as well as governments' experts.

Sa'udi Arabia. Starting with the countries in which easy control is possible, it has been found that this applies to Sa'udi Arabia. Owing to the limitation of transmission sites there, the control of infested foci by molluscicides is not difficult and the eradication even of infection is feasible in many areas (Arfaa, 1973). In most parts of the country the habitats of snails consist of wells, small canals, cisterns, small swamps, interrupted streams and ponds. In Gizan region,

prevalence was high, *Schistosoma haematobium* infection in children reaching 77%. *Bulinus beccarii* was found just 300 meters below the reservoir constructed in the Wadi (valley), near Messalah. In Medina city cisterns were found infested with *Biomphalaria arabica*. Prevalence of *S. haematobium* was 56.8% in 1973, due to the presence of *B. truncatus* in springs and wells watering the town.

Libya. This country is another example for the Oasis type of water. Schistosomiasis occurs in certain foci in its 3 provinces. In 1966. (El-Halawani, 1966a, b), I found *Biomphalaria alexandrina* to be the vector of *S. mansoni*, associated with a prevalence of 33%, in the Oasis of Tauorga. In a larger sample of the population, El-Gindi (1971), found a prevalence of 24.5%. In 1966, I found *Bulinus truncatus* in streams and irrigation channels originating from springs in Derna, associated with an infection rate of 8.5% among 6-9 year olds and of 6.6% among children 10-14 years old, while El-Gindi, in 1971, found this rate to be 30%. In Fezzan, I found (El-Halawani, 1967) the breeding places of the only species present, *Bulinus truncatus*, to consist of large concrete cylindrical reservoirs of 4 m in diameter and 1.5 m in height, receiving water from wells by motorised pumping. Prevalence among school children was recorded, in different localities, to vary between 11% and 85%, while El-Gindi has recorded a much lower rate (3.2%) in the general population. Copper sulphate was applied to 129 water bodies infested with *B. truncatus* and 4 were treated with Bayluscide. Only some of these habitats were found, after a long time, to harbour snails. Libya is another example, where eradication of Bilharziasis seems possible.

Tunisia. Since 1891 schistosomiasis is known to occur in Tunisia. In 1960 I visit-

ed Nefzaoua and recommended in a report submitted to WHO/EMRO (Halawani, 1960) that an expert be engaged to plan a comprehensive epidemiological-malacological enquiry and conduct a campaign against schistosomiasis. Dr. J.E. Azar (1967) surveyed the endemic area and submitted the same proposal. Dr. L. Rey, WHO epidemiologist-malacologist, started the project in 1970. He found the disease prevalence to vary from a low incidence of 0.2% in Tomber, to 69.9% in Djedida, 51.4% in Guttaya, 50.1% in Mansoura, and 33.2% in Lalla. The breeding places of *Bulinus* snails are deep artesian wells, artificial superficial ditches, small springs known under the name of Arab-sources (present in Kebili-Douz zone where they water the palm trees). They even breed in surface streams fed by the rains which may become dry during summer; in those which retain water the salinity becomes high.

Mollusciciding was carried out with Bayluscide in a concentration of 1 mg per litre. One application in September 1971 in the oasis of Guettaya has succeeded in destroying *Bulinus* snails until 1974 (Rey, 1974). All habitats (200) containing *Bulinus* snails were molluscicided, and as a result transmission was practically interrupted. Positive cases were treated with niridazole, 20-25 mg/kg body weight daily, for seven days. The campaign against snails protected 160,000 inhabitants of the endemic area against infection and re-infection. Rey (1974) considered that eradication of schistosomiasis from Tunisia is possible by keeping the efforts at an efficient level.

The Arab Republic of Yemen has an area of 7500 square miles, mostly mountainous. Arfaa (1971) gave background information supplied by former authors and reported the prevalence of *S. haematobium*, as observed by himself, to be 27%

in Sanaa and its surroundings, and 10% for *S. mansoni*, also giving figures for other localities. The snail habitats consist of large concrete cisterns and small streams; 33% of 121 breeding places were found to harbour *Bulinus contortus* and *Biomphalaria pfeifferi*, the former chiefly in cisterns and the latter in streams. It is thought that control of infection can be achieved by means of mollusciciding.

As previously mentioned, the second category of countries are those where irrigation units are separate and have dead ends. Snail infestation occurs mostly in the terminal ramifications. The units are subjected to dryness during the summer and there are no drains. Because such conditions are present in Iraq, successful control of schistosomiasis there stands a good chance.

Iraq. In Hor Rajab pilot project there was indication, according to El-Gindi (1968), that successful interruption of transmission had occurred after mollusciciding operations with sodium pentachlorophenate. However, in Iraq, where many separate new extensive irrigation projects are underway, the possibilities for the spread of schistosomiasis are increasing.

In the Hor Rajab project area, the reduction in prevalence has continued and this may be due to control measures. But such an assumption must nevertheless be accepted with caution because in two schools in the comparison area, prevalence rates have also fallen steadily (Teesdale, 1971). However, Baquir (1974) mentioned in his official report that transmission has been interrupted almost completely in the West Jahbeiji river area, i.e. the area under control in Hor Rajab pilot project, as no infection appeared in children below six years of age. Chemotherapy (using hycanthone) has been conducted by

Baquir on a large scale, uncured patients having been retreated after three months.

In Iran, the pilot project assisted by WHO was organised in the northern part of the Khuzestan plain. The breeding habitats of *Bulinus truncatus* consist mainly of borrow-pits and canals. According to Chu, WHO malacologist, Bayluscide proved superior to either sodium pentachlorophenate or copper sulphate, being non-toxic to handlers and considerably cheaper than the two former molluscicides. Also, there are advantages in mass treatment, because the endemic area in Iran is small; in some villages transmission sites have disappeared and in some infected areas snail habitats are unstable (Arfaa et al., 1967). In Iran Niridazole was the drug used in an attempt to control *S. haematobium* in 14 villages. The daily dose used was 30 mg/kg body weight for four consecutive days. The mean prevalence of infection before mass chemotherapy was 39% and 3-5 years later it was 14% (WHO Expert Committee 1973).

Lebanon. In 1962 I had the opportunity to conduct a survey and delineate the area where *S. haematobium* is endemic: in Sarafand and neighbouring villages. I submitted a plan for a pilot project, after determining the rate of prevalence and finding the breeding places of *Bulinus truncatus* (El-Halawani, 1962). The snail intermediate host was previously also reported by Dr. Azar and collaborators during their survey*. Abdallah (1963) was delegated as WHO short term consultant to Lebanon, where he organised the pilot project and conducted training of the national staff. El-Bitash (1969) stated in his evaluation report that in Sarafand and surroundings the prevalence rate dropped from 5.3% in 1963 to 0.27 in 1968. The total number of persons

examined was 24,028 during the whole period (1963-1969). The most characteristic habitats of snails are the siphons and irrigation channels. The measures carried out were mollusciciding and treatment of infected individuals with Ambilhar. Efforts in helping the people of the endemic area to get safe water in their houses had a great influence on lowering the incidence of the disease. According to Hamami (1975), there are no indigenous cases reported among Lebanese; infected cases were only detected among labour immigrants coming from foreign countries.

Syria. According to Abdallah, 1965, the combat against bilharziasis in the WHO pilot project which was started in 1954 can be differentiated into two periods. During the first five years, treatment of the infected population and the systematic application of molluscicides to infested streams were regularly carried out and a very significant reduction in the prevalence of the infection was obtained. Since 1960, however, the only control measure properly accomplished was a regular house to house survey and consequent treatment of infected individuals. The concentrated efforts towards the treatment of patients has led to a further, though much slower and less marked, decrease in prevalence rate. Transmission of the disease has as yet not been prevented.

Egypt. The effectiveness of molluscicides has been demonstrated in Warraq el Arab, Egypt, in a cooperative project of the United States ICA and the Research Institute for Tropical Diseases, Cairo. By introducing sodium pentachlorophenate 2-3 times a year into the main canal and maintaining a 10 ppm concentration for 8 hr throughout the system of irrigation canals that supplied water to an area

* Quoted by El-Halawani (1962), El-Bitash (1969), and others in their reports to the WHO.

covering about 25 km² and with a population of about 50,000 people, it was possible to control the snails and the transmission in the area (Wright et al., 1958). The prevalence of *S. haematobium* and *S. mansoni* in 6-year old children at the beginning of the experiment was 13.2% and 1.5% respectively. Five years later, among children who were two years of age when the experiment began, 2% had *S. haematobium* and 0% had *S. mansoni* (McMullen et al., 1962). The success of mollusciciding operations in this project could also be attributed — as I had opportunity to observe when acting as the national counterpart in the team carrying out the control measures — to the adequate removal of vegetation from all drains.

As to the pilot project called Egypt-49 and assisted by WHO, it was started in 1960, with the chief objectives of designing and testing control measures to determine the most effective and economical means of controlling schistosomiasis under conditions prevailing in Egypt. The project area is situated in fairly typical Nile Delta country in Beheira province near Alexandria. In 1964, mollusciciding was initiated in the form of a blanket application over the whole of the operation area in the spring, with a second blanket application in the autumn. After two years the mollusciciding programme was changed, the spring blanket application was followed by a surveillance programme in the autumn; the molluscicide was being applied wherever live snails were found.

Three years after the start of mollusciciding an interim assessment revealed the following findings:

In the operational area none of the children, born since the beginning of mollusciciding, were found infected with

Schistosoma haematobium, whereas children of the same age who lived in the comparison area were infected. This was satisfactory. Data for *S. mansoni* infection were also satisfactory, but here there was a complication, for apparently prevalence of *S. mansoni* infection had decreased spontaneously during the period of observation in the whole of the project area.

Forsyth (1970) used two main measures in assessing the effectiveness of molluscicide application as a means of controlling schistosomiasis: (1) Prevalence in samples of children 0-6 years of age, and (2) prevalence in population samples. Comparison between base-line, pre-mollusciciding and post-mollusciciding data was made. Findings in operational divisions, in which molluscicide was applied, were also compared with those in the comparison or control division, in which no molluscicide was applied. The effect of mollusciciding in controlling urinary schistosomiasis in some villages was also measured by comparing urinary egg counts of children 0-6 years old in successive years before and after the start of mollusciciding. This is based on the finding that if transmission continues at the same level as before, children who are now in age group 4 (i.e., the last birthday being four years) will in one year's time have an egg output similar to that of children in age group 5 (last birthday five years). For measuring this parameter, it is advised by Bell et al. (1967), that the original random selection of villages should be abandoned in favour of deliberate selection of more villages in which transmission level is high, as this ensures the largest return in terms of effect invested.

In conclusion, Forsyth (1970) stated that after encouraging preliminary reports published in 1966 by Farooq &

Nelson, the findings of the 1968 and 1969 3rd quarter report were very disappointing, for they showed that, although prevalence of schistosomiasis fell in the project area between the periods of 1962-1963 on the one hand, and 1968-1969 on the other, the improvement was not greater in the operational, or molluscicided, divisions than it was in the comparison (control) division, where no molluscicide had been applied. The improvement cannot therefore be attributed to the effects of mollusciciding; indeed in part of the operational area there was an apparent increase in prevalence of schistosomiasis between 1962 and 1969, despite the continuous programme of mollusciciding in the interval. The project has shown that the methods of molluscicide application which were used in operational areas were ineffective in controlling schistosomiasis.

Gilles, in his 1970 evaluation report on the same project (Egypt-49), concluded from the high conversion rate in the molluscicided area that, if mollusciciding had been at all effective, the interruption of transmission achieved must be low. He used three parameters to evaluate the effect of mollusciciding on transmission in the project area:

- 1) Conversion of negative to positive cases (from children that had been 0-6 years old in 1963 and that are still available in 1970).
- 2) Prevalence of infection in the 2-6 year age groups.
- 3) Incidence of infection in the 2-6 year age groups (1970-1971).

He found that the total conversion from negative (1962-1963) to positive (1970) in children aged 7-13 years in 1970 to be 82.1% in the molluscicided area while it was 72.2% in the comparison

area. In 1971, he found prevalence in children aged 2-6 years in the molluscicided area to be 44.6%, while in the comparison area (excluding Akrisha, a semi-urban rather than rural area, where it was 24%) prevalence was found to be 33.5%. He concluded «that the relative failure of mollusciciding as a single method of control does not cloud the very real benefits achieved by the project during the past years providing, as it has done, unique information on the epidemiology of schistosomiasis in the Nile Delta, the population dynamics of the vector snails and evaluation parameters for schistosomiasis control projects throughout the world. It is more than likely that a combination of mollusciciding and human treatment will prove the most effective way of controlling schistosomiasis in the Nile Delta».

Chu, WHO adviser (malacologist), states in his report on project Egypt-49 (Chu, 1972) that the snail situation was not known in the summer after blanket mollusciciding had been carried out in April or Spring. Results obtained in 1968-1969 showed that the number of *Biomphalaria alexandrina* had increased in August to five times the number that were present in April, and the number of *Bulinus truncatus* had increased from 2-5 fold that occurring in April after one blanket mollusciciding had been carried out in May. Moreover, after carrying regular snail surveys from 1967 to 1969, it was found that Mahmoudiah canal, which was thought to contribute very few snails to the main canals in the project area, was infested along its banks, and that it was the important source for the snails that had re-infested canals in the molluscicided area. Thus, main canals should be treated more frequently than twice a year. In small drains which constitute about 60% of the total length of

the water courses in the project area, snails are easily detected, but not easily killed by a single mollusciciding, because of severe water fluctuation; however they may possibly be killed by frequent treatment.

For these reasons, a new mollusciciding programme was started in January 1970 which involved the following yearly schedule: 1) From the 16th of May to the 15th of November, snail surveillance and mollusciciding of infected water courses every 45 days. 2) From the 16th of November to mid-April, snail surveillance without mollusciciding. 3) From mid-April to the 15th of May, mollusciciding of all water courses found positive during the period from the 16th of November to mid-April (i.e., the preceding five months when transmission is minimal). 4) Similar rotation surveillance surveys were carried out in the comparison area where no mollusciciding was done. A total of six tons of Bayluscide was used during 1970. The population of *Bulinus truncatus* was reduced by 99% in June, 95% in July, 99% in August, 98% in September-October and 100% in October-November in the molluscicided area (Kom El-Berka and Kom Ishu). The population of *Biomphalaria alexandrina* was reduced by 88% in June, 74% in July, 32% in September and 54% in October-November, but increased by 11% in August in the molluscicided area.

After the application of the new mollusciciding programmes, Gilles (1972, 1973) stated in his third evaluation report that not a single infected *Bulinus truncatus* was found in the molluscicided operational area throughout the three years of observation, yet transmission was still clearly going on.

Three parameters have been used for human evaluation of the new molluscicid-

ing programme: (a) Conversion studies. Here, children 2-6 years old who were negative in 1970 were reexamined in 1972. (b) Prevalence of infection in a growing cohort of children. (c) Prevalence of infection in the age-groups 2-6 years.

Dr. Gilles, after analysing his data, concludes that the only clear-cut difference in prevalence rates in 1972, in children aged 2-6 years occurred in villages where the prevalence of *S. haematobium* infection was initially high (> 50%). On an area-to-area basis, as well as in villages of moderate (25%-50%) and low endemicity (< 25%), the effects of mollusciciding are very unimpressive.

Fayoum. A large programme in the Fayoum Governorate of Upper Egypt utilising chemotherapy and molluscicides caused interruption of transmission. This is a project (conducted by the Ministry of Health of Egypt assisted by the Federal Government of Germany) which will be the subject of a special paper to be delivered in this plenary session by Dr. A. Mobarak.

Concluding Remarks

In conclusion, I would like to draw attention to the fact that schistosomiasis has not so far been satisfactorily controlled with one single measure even in countries with limited endemic areas. As it has been emphasized in this contribution, countries have already combined mollusciciding with chemotherapy because mollusciciding alone has failed to interrupt transmission satisfactorily. Sanitation and education should also be considered as effective measures against the spread of schistosomiasis. Wright et al. (1958) stated that, in so far as the Middle East is concerned, it will be decades, if not generations, before control of bilharziasis can be accomplished through ap-

plication of environmental sanitation. Contrary to this statement, I believe that provision of potable water for drinking, washing, and bathing pools will distract people away from infective water courses. In Egypt a large proportion of villages receive potable water free of charge and some inhabitants have procured piped water in their houses at their own expense. At present rural inhabitants are constructing their own latrines or requesting their construction from official funds. Water facilities for domestic use and bathing will draw people away from canals and thus limit contact with infected canal water. In St. Lucia (Windward Islands) piped water was supplied to five villages in 1970. The prevalence, incidence and intensity of *S. mansoni* infection and the frequency of human contact with water at the streams were recorded in the test area and in a comparison area, starting two years before the water supply was installed. During the 12 months after the water supply became operational there was a very marked reduction in human contact with the stream system; the number of contacts fell by 82%, the contact time by 96%. Reduced prevalence and incidence among infants was preliminarily reported from one village (Report of WHO Expert Committee, 1973).

Sanitation and modern utilities can be achieved in rural areas by constructing rural townships to replace cluster villages neighbouring one another. It is feasible to study right now such a plan for the future evolutionary development and modernisation of rural areas.

Usually countries in which schistosomiasis is endemic are short of funds for financing effective control of the disease. The lack of specific adequate budgets impede progress in the control of schistosomiasis. Also lack of statistics in respect to the problem makes governments reluctant to give support and thus the problem is relegated to low level priority.

The problem of schistosomiasis urgently requires concerted national and international action, because as previously mentioned, shortage of hard currency often stops or lessens the importation of drugs and chemicals required for treatment and mollusciciding. Therefore, it is strongly recommended that special funding programmes for the control of schistosomiasis should be given high priority by the national governments concerned and by international organisations, namely WHO, UNICEF, and FAO.

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REALISTIC GOALS IN THE USE OF MOLLUSCICIDES IN DIFFERENT ENDEMIC AREAS OF SCHISTOSOMIASIS

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Introduction

1. **Molluscicides in the Control of Schistosomiasis**

Snail control by the use of chemical agents has been advocated because they are expected to produce quick and considerable reduction or eradication of the molluscan hosts of schistosomiasis and would thus reduce or stop transmission

of the disease. This control measure can be executed with little or no active collaboration of the local community, a collaboration which is essential for other control measures, and which in practice is very hard to obtain.

Chemical control of snails has failed in some areas, and the results have been attributed to the great differences in the type of habitats treated, to differences in the susceptibilities of the various species and strains of snail hosts, to inadequacy of the equipment used, to the crudeness of the methods of application, and to shortage in skilled personnel in charge of the mollusciciding operation.

Control of human schistosomiasis through the use of molluscicides has the added advantage in certain areas of destroying and controlling the associate snail hosts of other snail-borne diseases of economic importance. Such are diseases of domestic animals, namely fascioliasis (which infects cattle, sheep, goats, and can also infect man), animal schistosomiasis (affecting cattle, sheep, equines, camels, and also possibly man), paramphistomiasis (of cattle, sheep, goats), and gastrodisciasis (of equines). Molluscicides which exhibit herbicidal and insecticidal properties are advantageous in rendering several benefits. Thus, in the cost/benefit analyses of control operations for the control of snail-borne diseases in an area,

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one should include the control of other diseases which are transmitted by arthropod vectors and the control of undesirable aquatic weeds. Molluscicides will no doubt play an important part in integrated control of schistosomiasis in the foreseeable future, as judged by the scientific advances in the development of these chemicals, and the documented reduction in the prevalence of the disease in certain countries where they have been used.

2. Progress in the Field of Chemical Control of the Snail Hosts

Snail control by molluscicides has had the advantage over work with other pesticides, because, for the last two decades, it has been stimulated and *coordinated* through the intermediary of an interested health agency, the World Health Organization. The progress has been achieved as a result of WHO-supported laboratory and field investigations and of the stimulation of the industry by WHO. Accordingly, the methods of evaluation, and the criteria adopted have attained a higher degree of *uniformity* among different workers, and in different countries, than are found in any other discipline in the field of pesticide research. Control of schistosomiasis through the use of molluscicides remains the measure of choice either alone or in combination with habitat management or chemotherapy.

The progress in the field of molluscicides is evident by the fact that new molluscicides have been found by the industry, and are available on the market; and that new formulations of the new and old chemicals have been developed to facilitate application and to increase efficacy. At present we have a number of satisfactory formulations which are effective against the snail hosts at very low concentrations, and at the same time, as

far as is known, exert a minimum effect on the biota. Other advances have been made in developing practical, easy and effective methods and equipment for application; use has been made of aerial «ultra-low volume» application (Sturrock & Barnish, 1973; Amin, 1974) and of slow-release technology (Cardarelli, 1974; Castleton, 1974). Prolonged, if not continuous applications are now possible through the use of liquid concentrates and solid formulations. Prolonged applications make possible a multi-measure attack against schistosomiasis, including effects on all stages of the snail, as well as on the larval stages of the schistosome parasite in the water. Moreover, methods have been developed to determine the dispersion of molluscicides in flowing water (Paulini & Paulinyi, 1971). Choosing a molluscicide to be used in a certain endemic area involves a number of criteria. For an objective decision, Jobin (1968) developed a mathematical model which compares molluscicides on a rational basis, and the model takes into consideration data on toxicity, stability, labor costs, and hydraulic characteristics of the body of water to be treated.

Goals of Mollusciciding

The important role which molluscicides play in the control of the disease has been documented by data obtained from successful projects in Tanzania, Egypt, Japan, Rhodesia, and Ghana, where molluscicides alone produced a marked impact on incidence of the disease. In Brazil, near Belo Horizonte, in Rhodesia, in the Kyle catchment, and in Egypt, at Warraq El-Arab, there has been evidence also of decrease in prevalence. Molluscicides were also effective in combination with chemotherapy in Cameroon, Khuzestan (Iran), Madagascar, Rhodesia, Fayoum (Egypt), and near Mochi and Misungwi (Tanzania). In Japan and in the

Philippines they were used successfully together with environmental snail control measures. In Puerto Rico they were effective in reducing prevalence during the last two decades. However, other factors helped in reducing human-water contacts. The data obtained from these various countries are summarized later on in this paper.

The success of the above projects has been attributed to the fact that they started with well-defined and realistic goals, with an understanding of the nature of transmission in the area, that consideration was given to characteristic local conditions, budget, personnel, procedures, technical difficulties and evaluation methods. Reducing transmission to an extent where the disease is no longer a public health problem, or reducing intensity of infection, are more realistic goals in many endemic areas than would be the eradication of the disease, which can only be attained in a few small areas, for example in limited foci in arid zones and on small islands. Other reasons for success of the control projects listed above are that feasible strategies, such as the type of control and timing of molluscicide applications were developed. Moreover, the goal was fulfilled because there was no change in the adopted strategy and there was no relaxation in the regular schedule for molluscicide application.

An understanding of the nature of transmission in an area is very important in achieving the goals set. Since transmission of the disease depends on climatic and hydrological circumstances it follows then that such factors should be first determined, before embarking on control operation. The ecological factors which condition the habitat of the planorbid snail hosts have been dealt with previously (Malek, 1958a). It is recognized that the factors vary from one area to another.

In some parts of the Egyptian Delta, in Syria, and in Lebanon there is a considerable reduction in the populations of the snail hosts during the winter, when new infection with schistosomes and other trematodes becomes minimal. Human contacts with the water are also minimal. Mollusciciding operations during this period are no doubt unnecessary. The situation is different during the spring and summer, where climatic factors favor the building up of stable snail populations and their infection, and when the human-water contact is usually optimum.

In some natural habitats in tropical areas climatic conditions such as lack of rain limit the snail populations and the human-water contacts. During such periods mollusciciding is also unnecessary. In irrigation schemes, flood waters loaded with silt for a few months limit aquatic vegetation and snail populations, and the silt contained in them interferes with the efficacy of several molluscicides. During other seasons, when conditions favor transmission, the goal of mollusciciding is usually to reduce or eliminate the factors which cause transmission. It is in the context of these statements that the concept of focal control has received attention and proved practical in some areas as will be indicated below under Strategy.

In some endemic areas one of the goals of the use of molluscicides is the reduction of morbidity of the disease among the population. In this respect beneficial effects of molluscicides have been demonstrated in Egypt. In spite of the fact that the use of molluscicides for control in certain parts of Egypt has not reduced the prevalence of the disease, fewer cases of overt disease and marked manifestations are now seen among the patients. A similar conclusion can be drawn in the Sudan Gezira where control

measures have been in effect for some years. Although not precisely documented, observations show that fewer severe cases are seen in the Gezira area, as compared to the White Nile reservoir area, in the same country, where no control measures have been, or are being, undertaken. Although it is realized that the relative severity of the disease is difficult to evaluate, it is nevertheless possible to assess the severity of symptoms from clinical, morbidity, mortality and autopsy records.

As indicated above, the goal of eradicating schistosomiasis is usually not a realistic one, except in a few situations. The reasons for this are mainly the extensive areas over which transmission is in operation and the fact that, in practice, it is very difficult to eradicate, in a given area, all stages of the snail hosts, as well as their eggs. What is possible is to kill the majority of the snails, but the few remaining ones are sufficient to repopulate the habitat if control operations are interrupted. In addition, there is also the possibility of the introduction of snails from nearby areas through the flow of water and the agency of humans and/or animals. Thus only a degree of interruption of transmission will remain the realistic goal of control in the situations existing in most endemic areas. As already stated, the few endemic areas where eradication of the disease is a realistic goal are certain small foci in arid zones and a few small islands. «Oasis Schistosomiasis» is found in certain countries of the Middle East. A good example of this type of schistosomiasis which lends itself very well to eradication is the Dakhla Oasis in the western desert of Egypt, where application of CuSO_4 was carried out in 1927 (Khalil, 1930). Repeated application of the molluscicide had eradicated the snail host *Bulinus truncatus* by 1952. Other

oases in Egypt, in Saudi Arabia, in Libya, Tunisia and Morocco and certain isolated foci in Kordofan and Darfur Provinces in the Sudan fall under this category of endemic areas where eradication is possible. The island of Vieques near Puerto Rico is an example of a focus where effective control measures can eradicate the disease (Ferguson et al., 1968). All evidence point to possible eradication of schistosomiasis on the small Caribbean island of St. Lucia. Malaria was eradicated on this island, and in the early 1960's the Pan American Health Organization was preparing for a control or an eradication program of schistosomiasis on the same island before the Rockefeller Foundation decided to utilize the island for research activities on schistosomiasis. Both are legitimate objectives.

With regard to some reasons for not achieving the goal in some control projects in spite of early successful results, the WHO-supported Egypt 49 is usually given as an example. Here, convincing interruption of transmission was demonstrated during the first four years of the project; the unsatisfactory later results were attributed to changes in the fundamental strategy of molluscicide applications, and related administrative factors (Gilles et al., 1973; WHO, 1973).

Strategy for Control

On the basis of studies in several countries we now have a better understanding of the most efficient strategy for successful control through the use of molluscicides, and thus for achieving the goal; we also have a better understanding of the reasons for the failure of mollusciciding operations. For each endemic area a strategy has to be developed for the use of molluscicides in the control of schistosomiasis, with the goal of reducing transmission efficiently. We have describ-

ed the necessary prerequisite studies before, during and after a mollusciciding operation, on the basis of which a strategy can be developed (WHO, 1965b). Thus a thorough knowledge of the natural history of transmission in a certain place is necessary. This will require a study, throughout the year, of the life history of the snail hosts, of climatic conditions, fluctuation in snail infection rates, and of human-water contacts. Such studies will determine the type and timing of the mollusciciding operation to be used, in order to obtain the best results, that is, the highest snail kill, and to prevent or reduce the repopulation of the habitat with snails.

Localized reductions in snail populations may be as, or more, effective as reduction in the entire habitat, if transmission is seasonal or restricted to certain foci. If molluscicides are applied only to such foci, even if repeated applications are found necessary, the procedure may be cheaper than treating the whole habitat. This strategy, first applied in Egypt, has also been undertaken and found effective and cheap in certain other countries.

In Egypt the method started in the early 1950ies as a matter of necessity. Whatever relatively small amount of molluscicide was available was applied to possible infection foci. It should be noted that the method had its shortcomings in certain areas of Egypt (Ayad, 1961). However, through the findings of the joint WHO/Egyptian Ministry of Health Pilot Project at Mena Area, Giza, most of the shortcomings of the method were overcome. It was demonstrated in the latter project that the majority of infected stations and of infected snails occurred within a radius of 500 m around inhabited places. Within that radius, infection of snail and man is expected to occur, particularly as regards children and adoles-

cents who, from a medical and social standpoint, are the sector of the population which stands in greatest need of protection.

In the Sudan Gezira, in the 1950ies, when I made my observations, considerable reduction in the snail host populations was mainly due to focal application of molluscicide (CuSO_4) based on snail surveillance, rather than to the maintenance dose of 0.125 ppm of the same molluscicide.

Focal control was effective when it was used in the WHO-supported Egypt-49 project, an irrigation scheme (Dazo et al., 1966), and in natural habitats in Rhodesia (Shiff & Clarke, 1967), Puerto Rico (Ferguson et al., 1968) and St. Lucia (Sturrock, 1973). The interval between two successive focal applications of the molluscicide varied from a month to 6 weeks, but differed from one area to the other depending on snail repopulation rates and the expected incubation period of the schistosome in the snail. The latter period is influenced by environmental factors, mainly temperature.

It has been repeatedly recommended that, for natural drainage systems, focal treatment, as a control strategy, must be preceded by the control of the entire watershed. It is realized that to control an entire drainage system is a difficult undertaking. It is time consuming and costly at the beginning, but it offers a possibility of eradication of the snail hosts. What would eventually happen in these areas is that such a control programme would later be limited to surveillance and focal control. These conclusions are based on my observations on natural drainage systems in St. Lucia, in several parts of Brazil, in Venezuela and in Puerto Rico. In St. Lucia, however, there are certain watersheds where focal control is

adequate without preceding control of the entire drainage system. On St. Lucia, marginal swamps and small tributaries just below the swamp origins are the breeding foci of the snail host, although not necessarily the sources of infection to man. Cercariae washed down from the snail breeding foci to the main streams cause human infections. After having studied the situation, determining the distribution of the snail host, *Biomphalaria glabrata*, and its various types of habitat, as well as that of associate snails on this Caribbean island (Malek, 1962b, 1975), I pinpointed many of the breeding foci and recommended a strategy for control which involved engineering measures only for certain habitats and the use of molluscicides for others (Malek, 1962b, 1963). The merit of the strategy advocated was subsequently demonstrated by my studies through 1965 and confirmed by Sturrock (1973).

Gravity or pump irrigation schemes do not present the difficulties offered by natural drainage systems. Blanket mollusciciding is applied at the head of the main canal or canals and the chemical, with the exception of copper sulphate, will proceed downstream with the flow of water. If the strategy is to follow blanket application by focal control, attention should be given to repopulation of the treated areas by snails from other sections of the system.

Large reservoirs and lakes represent snail habitats where the logical strategy is to adhere to the concept of focal control. The large volumes of water in these water bodies prohibit blanket application of molluscicides. By thorough surveys, heavy concentrations of snails can be located and molluscicides applied to these areas alone, perhaps preceded by certain engineering measures. Man-made lakes have come in the picture in recent years

and are good examples for the application of the focal control strategy. Such lakes threaten to aggravate preexisting low prevalences of the disease. Among these lakes are, in Africa, Kariba Lake between Zambia and Rhodesia, Volta Lake in Ghana, Kainji Lake in Nigeria, and Lake Nasser in Egypt. Here again, a realistic goal should be to reduce the snail populations to an extent that will interrupt transmission. An unrealistic goal would be to attempt eradication of the snails in such large lakes. The subject of schistosomiasis control in man-made lakes is included in a pamphlet which I prepared for a WHO/United Nations Development Programme (WHO, 1968a).

Lake Kariba on the Zambezi River began filling in toward the end of 1958, and reached its maximum extent in 1963. The lake lies approximately North-East/South-West in the middle section of the Zambezi between Zambia and Rhodesia. It has a surface area of about 2,000 square miles, a maximum depth of 120 m (average 45 m), an approximate length of 168 miles, and a storage capacity of over 130 million acre-feet. The prevalence of both *Schistosoma haematobium* and *S. mansoni* has increased in the lake area, with *Bulinus (Physopsis) africanus* and *Biomphalaria pfeifferi* acting as the snail hosts (Hira, 1970a ; 1970b). The Akosombo or Volta dam, constructed on the Volta River in Ghana is 130 m high, has an area of 3400 square miles and a gross capacity of 120 million acre-feet. Since 1964 there has been an increase in the population of the snail *Bulinus truncatus rohlfsi*, in aquatic vegetation, and in the prevalence of urinary schistosomiasis (Paperna, 1970). At present there is a special WHO team collecting excellent baseline data on the extent and transmission of the disease and the distribution of the snail host with the objective of future control. The Kainji

dam on the Niger River in Nigeria was completed in 1968 and created Lake Kainji, which is about 570 square miles in surface area. The snail hosts of both *S. haematobium* and of *S. mansoni* are found in the lake, and transmission is taking place in settled areas. The Aswan High dam (Sad El-Aali), officially opened in 1971, created lake Nasser which has been filling since 1964. The dam is 127 m in height; the lake is 300 miles long, 90 m deep, has a surface area of 2660 square miles and a maximum capacity of 164 billion cubic m (127 million acre-feet). Transmission of *S. haematobium* is apparently now taking place along the shores of the lake, and populations of the snail *Bulinus truncatus* are present. No species of *Biomphalaria* have so far been found in the lake.

Outside Africa, the Pahlevi dam on the Dez River in the Zagros mountains in south-western Iran helps to irrigate 30,000 acres in Khuzestan and about 125,000 acres are underway. Fortunately *Bulinus truncatus* does not occur in the reservoir, or in the dam area in the mountains. Moreover, control efforts in the irrigated area downstream, between Dezful and Ahwaz have brought schistosomiasis to a low prevalence. In the Mekong River basin in Southeast Asia, four dams have been constructed and several others are projected. Reservoirs behind the Ubol-Ratana (Nam Pong) and Nong Wai dams, in northeast Thailand, do not harbor «*Lithoglyphopsis** *aperta*», the aquatic hydrobiid snail host of *Schistosoma japonicum* in the Mekong basin, i.e. in Laos and Cambodia. The reservoirs in Thailand, however, harbor *Parafossarulus striatulus* the snail host of the human liver fluke *Opisthorchis viverrini* (Harinasuta et al., 1970). In Brazil several

reservoirs have been established in the São Francisco River basin and several others are projected. The Superintendencia de Vale São Francisco (SUVALE), is in charge of the coordination of all the planned projects. A visit to the Baheiras region in the State of Bahia, in this river basin revealed to me the high prevalence of schistosomiasis mansoni and the abundance of the snail hosts *Biomphalaria glabrata* and *B. straminea*. Other medium-size and small reservoirs in the northeast, about 150 in number, established mainly for water supply, already harbor the snail hosts (Paulini et al., 1972).

Large swamps in some endemic areas also are a challenge. Inaccessibility is an obstacle in applying molluscicides to these habitats. Moreover, the large size of the areas which they cover render the application of chemicals prohibitive, and it would be more realistic to drain the swamps and utilize the land than to treat them with molluscicides.

The Jebel Awlia reservoir on the White Nile in the Sudan presents both lake and swamp conditions (Malek, 1958b). The lake extends for about 300 miles south of the Jebel Awlia dam. Large swampy areas, up to 1½ miles in width, exist along the banks of the reservoir. Having studied this reservoir between 1953 and 1959, I recommended to the Sudan Government not to attempt treatments during high water, that is, when the dam is closed, but to apply focal treatment of molluscicides during low water (April through June) when there remain in the swampy banks a number of ponds and creeks (Khors) which contain large populations of the snail hosts. The operation was thought to be worthwhile because the swampy banks provide transmission

* The snail has been provisionally assigned to *Lithoglyphopsis*.

sites for a number of affections, i.e., for human schistosomiasis (mainly *Schistosoma mansoni*, but to some extent also *S. haematobium*); for animal schistosomiasis due to *Schistosoma bovis* (which also infects man occasionally); for fascioliasis in cattle, sheep and goats due to *Fasciola gigantica*; for paramphistomiasis due to *Paramphistomum microbothrium* in cattle, sheep and goats and for gastroduodenitis, in equines, due to *Gastroduodenitis aegyptiacus*. The Sennar reservoir on the Blue Nile in the Sudan, which feeds the Gezira irrigation system, functions as a large aquarium for the breeding of several snail species, including *Bulinus truncatus*, and of several species of aquatic weeds. Pools containing snails are left behind after the water recedes. Although extensive control measures using molluscicides have been undertaken in the Gezira system, no control operations have ever been conducted in the reservoir which supplies the irrigation system with water.

The studies conducted on the Jebel Awlia and Sennar reservoirs serve as an example of what could be done regarding large reservoirs and natural and man-made lakes so as to help in the planning of control strategies in such large bodies of water.

There is a rich snail fauna in the Jebel Awlia reservoir, among which the following species are hosts of disease-producing trematodes of humans and animals: *Biomphalaria alexandrina*, *B. sudanica* (*Schistosoma mansoni*); *Bulinus truncatus*, *B. (Physopsis) ugandae* (*S. haematobium*); *Bulinus truncatus*, *B. (Physopsis) ugandae*, *B. forskalii* (*S. bovis*); *B. truncatus*, *B. (Physopsis) ugandae* (*Paramphistomum microbothrium*); *B. forskalii* (*Gastroduodenitis aegyptiacus*); *Lymnaea natalensis* (*Fasciola gigantica*). The distribution of the

snail hosts in the reservoir, together with that of aquatic weeds, was studied; the seasonal fluctuation in snail densities was determined as well as the infection of snails with human and bovine schistosomiasis and with other trematodes (Malek, 1958b, 1959, 1969). Variations in the size of the snail populations follow the schedule of opening and closing the dam. The capacity of *Bulinus truncatus*, *Biomphalaria alexandrina*, *Biomphalaria sudanica* and *Bulinus (Physopsis) ugandae* to transmit human and bovine schistosomiasis was demonstrated by infecting white mice in the laboratory with cercariae emerging from naturally infected snails, and recovering the adult worms later. Aestivation of the snail hosts after the reservoir water recedes was also studied in certain foci, as well as the survival of the schistosomes in some of the aestivating snails. The intestinal form of schistosomiasis is very common among the local population of the reservoir area, where prevalence rates range from 60% to 90%. Moreover, this is one area of the Sudan where clinical manifestations of schistosomiasis *mansoni* are very common, including hepatosplenomegaly, ascites and cor pulmonale.

One recent report from Africa includes the results of control of *Schistosoma haematobium* in crater lakes, that is, natural lakes. Duke & Moore (1971) used the molluscicide Frescon, in addition to human mass treatment with Ambilhar (niridazole), in the crater lakes of Barombi Mbo (2 km in diameter and up to 100 m deep) and Barombi Kotto (1 km in diameter, and not more than 20 m deep), both in West Cameroon. Results of the study demonstrated the feasibility of snail control at the edge of these water bodies and similar natural and man-made lakes, by using Frescon at 2 ppm once every 6 weeks, which controlled the snail host *Bulinus truncatus*

rohlfsi. Mollusciciding the foci of snail breeding and chemotherapeutic treatment of all egg-passers with niridazole resulted in a marked reduction of *S. haematobium* transmission.

The available evidence indicates that transmission of schistosomiasis is occurring in natural and in man-made lakes and reservoirs in Africa and elsewhere in the world, as well as in irrigation schemes which are supplied with water from them. Steps should be taken to initiate studies, with the objective of control in order to alleviate undesirable repercussions. This is deemed necessary especially as it is projected to harness the waters of several rivers, and as water development projects are planned in various countries.

Available and Potential Molluscicides

The classification as to «available» and «potential» is based on effectiveness, completeness of laboratory evaluation, field screening, field trials, demonstration of transmission control, and commercial availability of the product. On this basis Bayluscide (niclosamide), Frescon (N-tritylmorpholine), Sodium pentachlorophenate (NaPCP), and copper sulphate may be considered as «available molluscicides». A number of other compounds have good potentials. They have been subjected to laboratory evaluations and have also received limited field evaluation and field screening in a few endemic areas. Available and potential (candidate) molluscicides vary as to their chemical composition, properties, formulations, dispersion, and their suitability for application by certain equipment. A number of publications, mainly by WHO, dealt in detail with the properties, advantages and disadvantages of molluscicides (WHO, 1965a, 1965b, 1971, 1973; Ritchie &

Malek, 1969; Ritchie, 1973; Malek & Cheng, 1974).

There actually is a need for a variety of molluscicides, and for the availability of different formulations of the same molluscicide, because of the great variation in snail species, their habits and the nature of terrain and climate where the molluscicides are to be used. Moreover, there are variations in habitats of the snail hosts as to physical, chemical and biological features. It is therefore, necessary, before choosing and applying a molluscicide to be used in a certain area, to ascertain data such as the nature and size of the water body, water current velocity, type and amount of vegetation, all or most of the microflora and micro- and macrofauna, temperature, pH, and turbidity. A complete water analysis should be made and the susceptibility of the local snail hosts to the different time-concentration relationships of the molluscicide determined.

A compound is preferred if it is safe to handle; if it has a low toxicity to man and his domestic animals, to crops, fish and the biota in general; if it is active against snails at low concentration, if it kills not only snails but also their eggs; if it is stable in storage and in the water after it is used; if it is adaptable for use by simple, durable equipment or requires no equipment at all, because the method of application and equipment has a bearing on the side-effects of the chemical; if tests are available for measurement of concentrations in the field; and if it is cheap, because its use will influence the cost/benefit estimates of the control operation. The present products known to have molluscicidal properties have some of the above advantages; the available compounds in particular possess many advantages. The following is a summary of the properties of the mol-

luscicides available and of those of a few candidate compounds.

1. Available Molluscicides

Frescon (N-Tritylmorpholine ; Trifenmorph)

Originally known as WL-8008, the chemical is produced by the Shell Company. It is N-triphenylmethylmorpholine, but the triphenylmethyl portion is designated as «trityl», thus resulting in the name N-tritylmorpholine. The chemical is also known as trifenmorph. It has been very thoroughly investigated by the company and by several investigators in endemic areas. It is available in the following formulations: emulsifiable concentrates, water dispersable powder and granules, spreading oils, and baits. Analytical tests have been developed for field use. The emulsifiable concentrate is active on snails (but not on their eggs) at 0.1-0.5 ppm with 1-hr exposures, and at 0.01-0.05 ppm with 24-hr exposures. Prolonged applications for 7 days each month, at a very low concentration of 0.025 ppm has been shown to be very effective in irrigation schemes, because in this way, the compound (which is non-ovicidal) kills any baby snails hatching from the eggs. Mud, vegetation, and light do not affect its efficacy, though the latter is affected at pH values below 7.0 due to hydrolysis of the compound. The emulsifiable concentrate is stable in storage and in the field. Short-term experiments with rats indicated that it is not toxic to mammals. Studies with fish showed that the susceptibility of the latter depends on the species of fish, and that, in general, prolonged applications of low concentrations are much less piscicidal. Crops are not affected in spite of the fact that small

amounts of the active ingredient were detected in rice plants.

Frescon has been found effective against the aquatic planorbid hosts of schistosomiasis, and against amphibious and aquatic lymnaeid hosts of fascioliasis. Frescon is marketed on a fair scale in Europe for the control of fascioliasis. The snails do not seem to protect themselves against the chemical by such means as crawling out of the water and by secreting excessive amounts of mucus. Moreover they retract into the shell only slowly, except when high concentrations are applied, as do the oncomelanid snails in the Orient. Satisfactory results have been obtained with Frescon in Rhodesia, Tanzania, Egypt, and Brazil, References: Paulini (1964); Shiff (1966); Shiff et al. (1967); Crossland (1967); Dawood et al. (1966); Boyce et al. (1967); Yasuraoka et al. (1969); Fenwick & Jorgensen (1972); Gilbert et al. (1973).

Bayluscide (Niclosamide; Bayer 73)*

This compound, originally known as Bayer 73, is produced by the Farbenfabriken Bayer, Germany. It is the ethanolamine salt of 5,2''-dichloro-4'-nitrosalicylanilide. It was commercialized as a 70% wettable powder, for which the International Organization for Standardization (IOS) has recommended the name niclosamide. A liquid emulsifiable concentrate (25% w/v active ingredient) was later developed. In the laboratory it proved to be very effective against all stages of snails and their eggs and low concentrations (Malek, 1971). In this formulation it is more suited for field application because the wettable powder formulation tends to clog the nozzles of drip-feed equipment used in applying it.

* See also under Mollutox below.

The chemical acts quickly in low concentrations with about equal efficacy for 1- and 24-hr exposures (for *Biomphalaria*, 0.2-0.5 ppm in 24 hr, 1.0 ppm in 5 and 6 hr; for *Bulinus*, essentially the same; for *Oncomelania hupensis*, 0.5 ppm in 24 hr; for *Oncomelania quadrasi*, 0.4 ppm in 6 hr). Storage stability is satisfactory for about 2 years; and in the water it is stable for up to 7 days. The chemical is not irritating to snails (*Biomphalaria*, *Bulinus*, and *Oncomelania*) and they thus do not crawl out of the water to evade it. Its effectiveness is slightly affected by sunlight (specially in the tropics), by adsorption on mud, or, in hard water, by a high concentration of minerals. A pH range of 5-9, such as is normally found in natural habitats, has no effect on niclosamide. The compound has a very low mammalian toxicity, though it is piscicidal. Fish toxicities (LC_{50}) vary from 0.05 to 0.3. Bayluscide has no herbicidal activity, and sugar cane, mustard, oats, and rice were not affected by it. It has been used with good results in Tanzania, South Africa, Iran, Egypt, Rhodesia, Puerto Rico, and the Philippines. References: Gönner (1961), Dawood et al. (1965, 1966), Shiff (1961), Pesigan (1967), Komiya et al. (1962), Abdalla & Nasr (1961), Clarke et al. (1961), Webbe (1961), Jobin & Unrau (1967), Ritchie et al. (1963), Ayad (1966).

Mollutox

Mollutox is the registered trade name of a homologue of the ethanolamine salt of 5,2'-dichloro-4'-nitrosalicylanilide, that is, Bayluscide (niclosamide), produced by the Chemical and Insecticidal Company, Abou-Zaabal, Egypt. The compound has already received laboratory as well as field evaluation. It proved highly effective against both *Bulinus truncatus* and *Biomphalaria alexandrina*; the lethal concen-

tration was 0.3 ppm at a 6-hr exposure. Field studies were conducted in certain governorates of Egypt, and a colorimetric test in water samples has been developed (Abdel-Rahman et al., 1974).

Sodium pentachlorophenate (NaPCP)

This compound and other related pentachlorophenols have been widely used for a variety of agricultural and industrial purposes, as wood preservatives, as termite deterrents, as weed killers, and as molluscicides. NaPCP is highly soluble and is available in the form of flakes, pellets and briquettes. Another solid formulation which has a longer release time than the briquettes (about 60 hr) has also been prepared. NaPCP is stable but is somewhat irritating when handled or applied improperly. It is ovicidal and molluscicidal to freshwater snails, but is less effective as an ovicide at molluscicidal concentrations against amphibious snails (*Oncomelania*). It used to be an effective and popular molluscicide for about 15 years in Egypt, Rhodesia, Japan, and Brazil before other molluscicides, e.g., niclosamide and Frescon, were developed. It is unaffected by the normal pH range of natural water; it is reduced by hard water and is irreversibly adsorbed by mud. Its effectiveness is reduced especially by sunlight, but also by high alkalinity and by adsorption on mud. In flowing water, exposures of 8-10 hr are effective at values of 50-80 ppm x h values. On moist soil it is applied at the rate of 4-10 g/m². It is a stable compound in storage and in the water, except for its photosensitivity. It has no herbicidal activity, but is highly piscicidal. Hazards in handling it were reduced by using briquettes, transferring them directly to metal baskets, without removing them from their containers. References: Wright et al. (1958); Meyling et al. (1959); Dawood et al. (1965).

Copper Sulphate

Copper sulphate is a stable, easy to handle compound, usually applied as a solution in aquatic habitats only. It has been used as a molluscicide since 1920, but its use is now limited to a few countries only. It is comparatively cheap, but 20-30 times the laboratory level must be used in the field because its effectiveness is reduced in the presence of organic matter, of certain types of dissolved solids and by a high pH. Its downstream carriage is very poor. It possesses herbicidal properties but is less toxic to fish than Bayluscide or NaPCP. It is now generally agreed that copper sulphate is too ineffective for major control efforts and cannot compete with other available products. References : El-Gindy (1953, 1957a,b) ; Ayad (1961) ; Malek (1962a).

2. Potential Molluscicides

Various compounds or natural products with molluscicidal properties are known. These have a varied combination of merits. But in addition to the fact that they have been subjected only to very limited field evaluations, most of them are not available commercially in large quantities. Most companies, however, have indicated that they are ready to produce relevant chemicals commercially, should a demand for them arise.

Yurimin (P-99)

Yurimin, a Japanese produce, is 3,5-dibromo-4-hydroxy-4'-nitrobenzene. Its performance has been satisfactory against both aquatic and amphibious snails. Eggs and newly hatched *Biomphalaria glabrata* in Brazil are more susceptible than adult snails. It is stable, unaffected by sunlight or water hardness, but an acidic pH of 4.5 to 5.2 decreases its efficacy. The compound is piscicidal (LC_{50} , 0.16-0.83 ppm), it has no herbicidal activity. Given orally it was acutely toxic to mice at 168 mg/kg.

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In laboratory and field tests in Japan it was shown to be several times more effective than NaPCP against the amphibious snail *Oncomelania nosophora*. References : Ijima et al. (1964) ; Paulini & de Souza (1968) ; Yasuraoka et al. (1968).

Insoluble Copper Compounds

Copper Pentachlorophenate. This stable, relatively insoluble compound, is obtained by mixing solutions of NaPCP and copper sulphate at a ratio of 2:1. It incorporates properties which far exceed those of the latter two compounds when applied separately. It is ovicidal and gives a residual effect in non-flowing water and on moist-soil habitats. It has proved successful in control operations for schistosomiasis in Venezuela and for fascioliasis in Australia.

Copper Carbonate. This stable product has been used as the molluscicide of choice for many years to control non-human schistosomes in lake habitats in the USA. It is applied at the rate of 36-60 g/m². It was proven effective in Brazil and on moist-soil habitats in the Orient.

Cuprous Oxide. This compound is slow acting and has a good residual effect when formulated as the stabilized «chevreul salt». Its efficacy has been demonstrated in Africa by Deschiens and his co-workers (Deschiens & Floch, 1968).

Organo-Tin Compounds

Several organo-tin compounds are effective agricultural fungicides, they also serve as major components of marine antifoulant paints, stabilizers for food packaging, and anthelmintics. Bis (tri-n-butyl-tin) oxide (TBTO), tri-n-butyl-tin acetate and tri-n-propyl-tin oxide have been proven to possess molluscicidal properties comparable to those of Bayluscide.

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Newly-laid eggs and newly hatched snails are especially sensitive to the effect of these organo-tins. They are stable compounds and are not easily affected by the physico-chemical features of the habitats. They are at present available as emulsifiable liquid concentrates and wettable powders. Organo-tins are especially suitable for slow-release formulations where they are incorporated in one of several elastomers, such as natural rubber, ethylene-propylene dimers, chloroprene and styrene-butadiene. One of these slow-release formulations is bio Met SRM, incorporating TBTO. For adult aquatic snails the LC_{50} (ppm \times hr) data are 0.9-1.3 for TBTO ; 0.5-4.0 for Frescon and 3-8 for Bayluscide. Deschiens & Floch (1968) regard tributyl-tin oxide and triphenyl-tin chloride among the six most practical molluscicides. Certainly results of field tests from the Sudan, Tanzania, Puerto Rico and recently from Brazil show that organo-tin compounds, whether applied by conventional methods or by slow-release methods, deserve to be included among the most effective and practical molluscicides (Castleton, 1974).

TBTO can be toxic to a number of freshwater fish, including *Tilapia*, goldfish and guppies, but is less toxic to larger fish such as bass, perch and others. The margin of safety for the sensitive fish over a 24-hr exposure appears to be about 0.03 ppm. TBTO had no effect on banana plants on St. Lucia.

Acrolein (Aqualin)

The compound is primarily a herbicide. Thus its application as a molluscicide is economical in irrigation schemes where there is a need to kill submerged aquatic weeds. It is molluscicidal and ovicidal at herbicidal concentrations. Its effectiveness has been demonstrated in the laboratory, and in field operations in

Puerto Rico, Egypt, Sudan, and Tanzania. It is a volatile, irritating (lacrimating) substance, but effective metering devices have been developed for applying proper dosages under the water surface and to protect the personnel making the application. Precautions must be taken, such as padding and transporting containers in covered trucks, to avoid explosions and to make its handling and transport safe in hot tropical climates (Hana & Malek, 1963 ; Unrau et al., 1965 ; Ferguson et al., 1965).

Paraquat (Gramoxone) and Diquat (Reglone)

These herbicides are both effective against adults and eggs of planorbid snails, at 4-6 ppm for 24 hr of exposure.

Carbamates

These compounds are primarily insecticides. At least three of them, namely, Rhodiacid, Sevin and Zectran (Ziram), have been tested as molluscicides in a limited way. These compounds, especially Ziram (Zinc dimethyldithiocarbamate), have been recommended for use in those countries where it is desirable to kill in the same water body mosquito larvae (in malaria and filariasis control), *Simulium* larvae (in onchocerciasis control), and *Cyclops* (against guinea worm infection or dracunculiasis). They are not toxic to fish but are relatively toxic to mammals (Gretillat, 1965).

Molluscicides of Plant Origin

Several plants, distributed in various continents, have shown molluscicidal properties. It has therefore been suggested that they should be grown alongside canals and other water bodies, so that the fruits or leaves would drop into the water and kill the snails. Another advantage of such plants is that they can be harvested and processed in endemic areas, and

would thus save the hard currency needed for the purchase of chemical molluscicides. It is also believed that molluscicides of plant origin might exert minimal effect on the environment, but this remains to be investigated.

Mozley (1952) tested a number of different vegetable substances against schistosome-transmitting snails, and listed the fruits of *Balanites aegyptiaca*, *Sapindus saponaria* and *Swartzia mada-gascariensis* among the most promising vegetable molluscicides. The active ingredients in the fruits of these African plants are known to be saponins. Saponins are glucosides. They form colloidal suspensions in water and are characterized by their ability to form foams in water. *Derris elliptica* and *Tephrosia vogelii* are other promising African plants in which the active ingredient is rotenone. The leaves, flowers and flower buds (and to some extent the stems) of *Tephrosia vogelii* have been found to be effective snail poisons. The roots of *Derris* spp., which are commonly used in the manufacture of insecticides, are also effective against snails. However, one disadvantage is that *Derris* is exceedingly poisonous to fish. In Egypt, the leaves and flowers of a herb, *Ambrosia maritima* (local name Damsis) have been reported to be molluscicidal (see also Shoeb & El-Emam, 1978). *Jatropha* sp. is another promising African plant known in the Sudan as «Habat El-Mollok». Its crudely ground seeds have been found to have molluscicidal potency (Amin et al., 1972).

Large scale laboratory and field evaluations have been conducted on *Phytolacca dodecandra*, an Ethiopian plant which is locally known as Endod, and is used by the natives as soap for laundering clothes (Lemma, 1970, 1978). Its active ingredient is a saponin. The berries are more effective than other parts of the

plant. Endod remains stable over a wide range of temperatures and pH values, in the presence of various concentrations of river bed mud and after ultraviolet irradiation of solutions. Its toxicity to mammals and plants has been shown to be very low. Lemma et al. (1972) reported enhanced potency together with butanol extract.

In Brazil several plants have been examined for their molluscicidal activity (de Amorim & Pessoa, 1962), and the following have been found to be effective, *Sapindacia*, *Paullinia pinnata* (locally known as «cruape») and *Stenolobium velutinum* (known locally as «tingui»). Moderate molluscicidal activity was noted with *Piptadenia macrocarpa* (known as «angico do campo») and a member of the Bromeliaceae (known as «gravata-acu»).

In China *Thea oleosa*, *Croton tiglium* and *Schima argenta* have been reported to possess molluscicidal properties (Cheng, 1971).

Methods of Application of Molluscicides

A brief section is included here on the methods of application of molluscicides because such methods are of significance in the degree of efficacy of the compounds applied, and might also have a bearing on the side-effects of these chemicals.

There are various methods of application. Selection of the most suitable method depends on several factors, including the type of snail habitat; its accessibility, especially if it is a water course or a swamp; the molluscicide formulation; the number of laborers available and the extent of their training; and the available funding of operational costs. In certain habitats simple equipment, such as spraying or dispersing gadgets, will

serve, or no equipment at all, for example in the direct manual application of the chemical. On occasion equipment for dispensing other pesticides, such as those used in agriculture, or in pest control and malaria campaigns, have been utilized in mollusciciding operations.

Spraying is one method for applying molluscicides ; it may be ground spraying or aerial spraying. For ground spraying the following equipment is in use : Hand sprayers, knapsack sprayers, spray pumps, and tractor-mounted sprayers. Such spraying equipment is suitable for stagnant or slow-flowing waters, for treating foci along banks of water courses where snails are abundant in order to supplement mollusciciding in flowing water, and for swamps and moist and wet habitats of certain planorbid snails, but especially for habitats of the amphibious *Oncomelania* spp. in the Orient, hosts of schistosomiasis japonica, and for the amphibious lymnaeid hosts of fascioliasis.

Ground spraying methods are preferred in many situations because they ensure that the chemical reaches the immediate environment of the snails. However, ground spraying is not feasible or economical in large bodies of flowing water such as the irrigation canals in large schemes, which may measure thousands of miles in length. In such cases, if spraying is desired, it is better undertaken by aircraft. The same holds true for large reservoirs and lakes, whether natural or man-made, the latter having assumed significance in the spread of the disease in various countries, such as Egypt (Lake Nasser), Nigeria (Lake Kainji), Ghana (Lake Volta), Zambia-Rhodesia (Lake Kariba), and the Sudan (several reservoirs). In such lakes and reservoirs a complete mollusciciding operation would be prohibitively expensive and unnecessary and ground spraying of

snail foci (focal application) where transmission has been found to be in progress, combined with some environmental control measures would be adequate. Aerial spraying has also been found convenient for lake shores ; it is, however, specially recommended for long irrigation canals, where it is feasible and economical. The method is, however, limited by wind and other obstacles such as trees and sluice gates. Aerial application was used in Rhodesia (Barnish & Shiff, 1970), in the Malagasy Republic (Degremont et al., 1972), in St. Lucia (Sturrock & Barnish, 1973) and in the Sudan Gezira (Amin, 1974).

Liquid feeders are especially suited for flowing water where the molluscicide is applied into a canal, at selected stations, so that it will be carried downstream. This way the considerable labor involved in spraying and dusting is saved. Several types of drip liquid feeders and gravity liquid feeders are available and have been widely used. Because of their simplicity, these feeders can be manufactured in many countries from available plastic or other material. The rate of liquid coming out of the feeder can be adjusted by a valve, or the like, so that the required amount, and accordingly the desired concentration of the chemical, can be dispensed. For prolonged applications of liquid formulations of molluscicides, feeders can be used at a single application point at the headwaters of the irrigation canal. Liquid concentrates were released effectively by this method in the Arusha-Chini scheme, Tanzania. In natural water sheds, liquid concentrates would have to be applied at several points.

With regard to solid formulations, copper sulphate crystals have been applied in jute sacs, both for an initial blanket treatment, and for a maintenance dose. It is the practice in the Sudan Gezira

scheme, to obtain a maintenance dose by placing the sacs at the intake of irrigation canals. Briquettes of NaPCP were applied in Egypt by leaving them in the shipping containers, and placing these containers in wire baskets at the canal intake.

Prolonged application of solid formulations has been greatly enhanced by their incorporation in matrices for slow-release. This term refers to the continuous long-term release of a chemical from an elastomeric matrix for a period ranging from a few months to several years. Several elastomers are used, for example, natural rubber, Neoprene (Chloroprene), Ameripol (Styrene-butadiene), Epcar (Ethylene-propylene dimer) and Acrylonitrile. Slow-release systems function through one or more of the following mechanisms: leaching, exfoliation and diffusion-dissolution.

Although the concept of prolonged applications, whether of liquid or solid formulations, was advocated and introduced early in the development of molluscicides, there are still very few data to prove their efficacy, as compared with short-term applications. Evaluation of slow-release organo-tins or Bayluscide in elastomer matrices has been carried out in some laboratories, but field evaluation was conducted in a few foci only, for example, in Brazil (Souza & Paulini, 1969; Castleton, 1974).

Some Control Projects where Molluscicides have been Used

Several control projects, stimulated or supported by United Nations Organizations, for example, WHO, UNESCO, UNDP*, and by National Governments provided significant information with

regard to molluscicides and their use in control. Moreover, acceptable data are now available which show the significant role which molluscicides play, alone, or in combination with other measures, in the control of schistosomiasis. Of significance in these projects were the realistic approach to the problem, and the strategies which were pursued in each project in order to achieve the goal(s).

1. Projects where Molluscicides were used alone

In a number of control projects (a-d) in which molluscicides were used alone there was a marked impact on the incidence of the disease. Examples of such projects are the following:

a) The WHO/Tanzanian Government Schistosomiasis Pilot Control and Training Project, at Misungwi, Mwanza District, Tanzania

The project, about 45 km south of Mwanza, was started in 1967 with the aims of determining the feasibility of control of schistosomiasis within present resources, and to develop control strategies which, with some modifications, might be applicable to other endemic areas in Tanzania and other parts of East Africa. The project area, where *S. haematobium* is endemic, is a rural area of about 118 km², with a population of 7,000. Pilot control operations are in the northwestern portion (about 76 km²; population about 4,000) which was divided into 5 sectors, in each of which different control measures, or combinations of them, were applied.

In the two sectors (Nos. I and IV) which had been repeatedly treated with Bayluscide (70% wettable powder formulation) since May 1970, and in sectors II

* United Nations Development Programme.

and III which had been treated with Bayluscide and by chemotherapy, there was a reduction in the rate of habitats positive for the snail host *Bulinus (Physopsis) nasutus*, a reduction which did not occur in another sector (No. V) where no molluscicide was used. Snail reduction was accompanied by a decline in the incidence of *S. haematobium*. These four sectors cover an area of about 68.7 km². It was estimated that the annual per capita cost of Bayluscide for three treatments per year was about Tanz. Shs. 1/30 (i.e., the cost of about 100 kg per 3,000 persons) (McCullough & Eyakuze, 1972).

b) Egypt-49

The WHO/UNESCO-supported Egypt-49 Project near Alexandria was started in 1960, with the main objective of designing and testing control measures to determine the most effective and economical means of controlling schistosomiasis under conditions in Egypt. The project

is about 220 km² in area, and has a population of about 250,000. Control of transmission was obtained during an initial 4-year period (1963-1966), in Kom Ishu (NaPCP in 1963; Bayluscide in 1964) and in Kom El Birka (Bayluscide in 1963 and 1964), as indicated in Table 1 (from Farooq et al., 1966). In Kom Ishu the incidence fell from 9.7% in 1962-63 to 2.0% in 1964-65, and in Kom El Birka from 7.5% to 1.8%. Gilles et al. (1973) reported a steadily declining prevalence (not incidence) in the same project amongst 0-6 year-olds in the years 1963 through 1966 (21.2%, 11.4%, 9.0%, 4.4%), but this was followed by an increase in 1967 (14.2%) and 1969 (22.6%). Thus the mollusciciding programme was initially effective but apparently control broke down around 1966 or 1967. It is believed that failure to achieve the goal after 1967, judged by the increase in transmission, is due to a change in the mollusciciding procedure and also to administrative reasons.

TABLE 1. Incidence of bilharziasis in children under 7 years old in two areas treated with molluscicide in the Egypt 49 Bilharziasis Control Project*.

Period of survey	<i>S. haematobium</i>		<i>S. mansoni</i>	
	No. negative at start	Annual incidence (%)	No. negative at start	Annual incidence (%)
Kom Ishu (NaPCP in 1963, Bayluscide in 1964)				
1962-63	45	20.0	52	9.7
1963-64	125	8.8	127	10.3
1964-65	138	9.4	139	2.0
Kom el Birka (Bayluscide in 1963 and 1964)				
1962-63	56	25.0	54	7.5
1963-64	148	6.1	162	3.1
1964-65	151	7.4	159	1.8

(*) From Farooq et al. (1966).

c) Rhodesia, Triangle and Hippo Valley Estates

Control measures instituted by the Rhodesian Ministry of Health were primarily directed against the large and widely distributed snail populations. A project area was chosen; it consisted of two large farming complexes; the Triangle Estate and the Hippo Valley Estate, together with a number of contiguous private farms, most of which are functionally a part of the Hippo Valley irrigation system.

Triangle Estate covers about 8,000 hectares watered by overhead sprinklers which are served by seven large reservoirs. The reservoirs are filled by gravity from the main canal. There are 12 sections using flood irrigation from 140 reservoirs. Man-water contact is extensive and habitats for *Biomphalaria pfeifferi* and *Bulinus (Physopsis) globosus* are plentiful. The Hippo Valley complex covers about 10,000 hectares, all watered by flood irrigation and includes 45 individually owned farms in which man-water contacts are very high. The population in the whole project area numbers about 70,000, of which some 25,000 are employed, the rest being dependents.

Bayluscide (Niclosamide) was used, either as a 70% water-dispersible powder, or as a 25% emulsifiable concentrate. The chemical was applied to the irrigation water by drip-feed methods once every 6-8 months. The drains, however, were treated routinely by pairs of rangers searching for snails and applying chemical where they were found. The efficacy of control operations was assessed by longitudinal studies in children free from infection to determine the incidence of infection. The results shown in Tables 2 and 3 indicate that transmission of both *Schistosoma haematobium* and *S. mansoni* was reduced to a level below that

measured in areas of Rhodesia where irrigation is not practiced. The total annual cost for the molluscicide operation was US \$ 54,800-55,500 (Shiff et al., 1973).

d) Ghana

The WHO/Ghana Government control project in the Wa District in North-west Ghana has had the advantage of several years of basic studies prior to embarkation on control. McCullough (1957, 1962) provided significant information on the transmission of *S. haematobium* in the project area. Later the use of molluscicide (Bayluscide) alone had an impact on the incidence of the disease (Lyons, 1972). The incidence after one year was 41%, and after two years 34%.

There are a number of other projects where molluscicides alone were used. No incidence data are available for these projects (e-h) but in the following there was a marked impact on prevalence of the infection (WHO, 1973) :

e) Brazil

In a project near Belo Horizonte, where niclosamide was used, the prevalence of the infection declined from an average of 23% to an average of 9% in two years.

In another project in Brazil where the evaluation of the mollusciciding operation was by egg count, the count declined to about 40% of the original value after four years.

f) Egypt

In Warraq El-Arab project, where NaPCP was used, the prevalence was also reduced in four years. This project started in 1953; the tract measured about 25 km² and comprised seven villages with a population of some 60,000 inhabitants, of whom 3,000 were school children 6-10 years of age. The project area became

TABLE 2. Data from controlled areas on Triangle Estate, Rhodesia, showing the incidence of *Schistosoma mansoni* and *S. haematobium* in cohorts of children under 6 years of age.

Date of Survey	<i>S. mansoni</i>				<i>S. haematobium</i>			
	Spray irrigation		Flood irrigation		Spray irrigation		Flood irrigation	
	No. negative*	incidence (%)	No. negative*	incidence (%)	No. negative*	incidence (%)	No. negative*	incidence (%)
Apr. 1968- Oct. 1968	54 52	3.40	65 63	2.77	64 63	1.14	55 51	5.25
Oct. 1968- Apr. 1969	69 92	3.65	77 64	16.03	112 110	1.24	83 78	4.46
Apr. 1969- Aug. 1969	103 101	2.39	63 59	7.25	115 112	1.34	70 69	0.70

(*) Results have been corrected where necessary for rate of loss of infection, incidence has been extrapolated to 120-day intervals. From Shift et al. (1973).

TABLE 3. Data from controlled areas on Hippo Valley Estate, Rhodesia, (flood irrigation only) showing incidence of *S. mansoni* and *S. haematobium* in cohorts of children under 6 years of age*

Months of survey	<i>S. mansoni</i>				<i>S. haematobium</i>			
	1969-70		1970-71		1969-70		1970-71	
	No. negative*	incidence (%)	No. negative*	incidence (%)	No. negative*	incidence (%)	No. negative*	incidence (%)
Feb.-June	130 121	8.72	154 133	17.19	192 187	2.61	220 210	4.55
June-Oct.	144 141	2.63	111 99	13.24	203 200	1.48	158 151	4.43
Oct.-Feb.	105 102	3.60	151 141	8.35	149 147	1.35	212 204	3.37

(*) Results have been corrected where necessary for rate of loss of infection. Incidence has been extrapolated to 120-day intervals. From Shift et al. (1973).

free from snails shortly after the first application of NaPCP in October 1954, but reinfestation took place from untreated canals upstream. Reapplication of the molluscicide was carried out three times a year throughout the project area, in addition to focal control of foci showing concentrations of snails. In four years, prevalence of infection among school children decreased from 40.2% to 23.7% in the case of *Schistosoma haematobium*, and from 5% to 1.8% in the case of *S. mansoni*. The decrease in prevalence was even more pronounced in the 6-year age group, where *S. haematobium* declined from 13.2% to 4.2% and *S. mansoni* from 1.5% to 0% (Wright et al., 1958). Subsequently the area became urbanized; a housing programme encroached on 3 of the 7 villages, the population increasing 10-fold as compared to 1953, when the project was initiated.

g) Rhodesia

In the Kyle catchment project, niclosamide was applied and the resulting decrease in prevalence varied in an age-specific way, from 1%-0 in children below 5 years of age, and from 34% to 12% in children aged 10-11 years over a 6-year period.

h) Tanzania

In the Arusha-Chini plantation in northern Tanzania, there was an impact on the prevalence of *S. mansoni* since 1968 by the use of molluscicides alone, even before the control efforts were combined with chemotherapy (hycanthone and niridazole). The estate is about 10,000 acres in size, with a population of about 5,000. It is owned by a Danish Company and is used for growing sugar cane. This irrigation system is one where experiments with control through the use of molluscicides have been conducted for a

number of years. This is the area where Crossland (1963, 1967) conducted his trials with Bayluscide and Frescon, and where Fenwick (1970) subsequently also worked. Only *Schistosoma mansoni*, transmitted by *Biomphalaria pfeifferi*, is endemic in this scheme. When I visited the estate in 1968, the procedure was to apply Frescon for 7 days each month at a concentration of 0.025 ppm. Later on the molluscicide was applied for a 5-day period every 7 weeks. The annual cost of this procedure was about US \$ 4,000. In addition, the drains present in the area were treated by Bayluscide at 4 ppm every 8 weeks, using knapsack sprayers, at a cost of US \$ 1,200 per annum.

2. Projects where Molluscicides and Chemotherapy were used in Conjunction

a) West Cameroon

Urinary schistosomiasis was controlled in a project in West Cameroon by the combined use of the molluscicide Frescon (N-tritylmorpholine) and Ambilhar (niridazole) for human mass treatment. The project area comprises the crater lakes of Barombi Mbo (2 km in diameter and up to 100 m deep), and Barombi Kotto (1 km in diameter and not more than 20 m deep). The population consists of 760 persons in 2 villages by the lakes, and of another 800 living in the hinterland.

The molluscicide was applied from a boat with a motor pump and a long delivery tube so that the chemical should reach the bottom of the lake and deliver a concentration of 2 ppm throughout the bottom 0.5 m of water. Shoreline stretches where snails and transmission foci had been identified were molluscicided, as well as a 50 m barrier on either side of them. The molluscicide was applied at 12-14 day

intervals to overcome the lack of ovicidal action of Frescon. This schedule was later changed to single applications every 6 weeks. A marked reduction in *S. haematobium* transmission was obtained in only a few months. The effect of control on human infections was assessed by a considerable reduction of live eggs passed by the population, and this was evident for 22 months after treatment (Duke & Moore, 1971).

b) Fayoum Governorate, Egypt

The project area included the whole governorate, which is isolated from the Nile Valley and irrigated by a single feeder canal, the Bahr Youssef. The governorate extends over 1,600 km², with a population of about one million. The control operation involved the use of Bayluscide (supplied by the Federal Republic of Germany together with the equipment needed) and the treatment of patients with Ambilhar (supplied by the Swiss Government). The Egyptian Ministry of Health provided the personnel, premises and the running expenses.

The goal of the project was achieved, because of a careful study of the hydrology of the area and a sound strategy for the application of the molluscicide. Thus the chemical was applied annually in spring and autumn to the Bahr Youssef, starting at a point 30 km upstream of its entrance into the governorate. This was done to ensure against reinfestation with snails from untreated sources. Bayluscide applied at 2.4 ppm to the Bahr Youssef was still lethal to snails (at 1 ppm or more) for a distance of about 114 km downstream at the end of that canal and in its ramifications. This strategy almost eradicated the snails between March 1969 and April 1972. Any snails appearing later were destroyed by focal application of the molluscicide and by a

spring blanket mollusciciding operation every year, wherever necessary. As a result transmission stopped. Because of the combined treatment with Ambilhar the overall prevalence rate of schistosomiasis in the governorate fell from 45.7% in 1968, before the start of the project, to 23.3% in 1971, and is reported to have subsequently fallen further to about 16% and still later to less than 10% (Ayad, 1974). There was even a more marked impact on the incidence of the disease, as judged by the examination of children up to 5 years of age. An additional advantage of the mollusciciding operation was the considerable reduction of liver fluke infections in domestic animals, between 1969 and 1971.

c) Tanzania

Two main control projects were operating in Tanzania, in which both molluscicide and chemotherapy were used.

(1) **Arusha-Chini.** The project area was described under b) in the preceding section on the use of molluscicides alone. Mollusciciding (Frescon and Bayluscide) was started in 1968 and was later supplemented with chemotherapy by the use of hycanthone and Ambilhar (niridazole). When the assessment was made in 1970, it was found that the annual incidence of *S. mansoni* among field workers had been reduced from 81% to 18%. In addition there was a marked reduction in the egg output of those workers who were still infected. Results of the prevalence surveys in adults and children are shown in Table 4; in young children up to 4 years of age, the prevalence of schistosomiasis mansoni was reduced to zero (Fenwick & Jorgensen, 1972). Evidence was presented through cost/benefit analysis that the whole control operation was economical and advantageous to the estate.

TABLE 4. Results of *S. mansoni* prevalence surveys carried out in early 1969 and late 1970 in the Arusha-Chini estate Tanzania*

Subjects	1969 survey			1970 survey			X ²	P
	No. examined	No. infected	% infected	No. examined	No. infected	% infected		
Field workers	175	103	58.9	176	55	31.3	25.9	0.001
Nonfield workers	87	31	35.6	88	13	14.8	9.04	0.01
Wives	114	32	28.0	107	15	14.0	5.70	0.05
Total adults	376	166	44.0	371	83	22.0		
Children aged								
0-2 years	44	0	0	29	0	0		
2-4 years	36	1	2.8	64	0	0		
4-6 years	39	6	15.4	43	3	7.0	0.74	NS
6-8 years	38	20	52.6	35	6	17.1	8.52	0.01
> 8 years	—	—	—	60	14	23.2		

(*) From Fenwick and Jorgensen (1972).

NS = not significant.

(2) **WHO/Tanzanian Government Pilot Project in Mwanza District.** The project area was described under a) in the preceding section. Sectors II and III of the project were used for the application of molluscicide (Bayluscide) and for the chemotherapeutic treatment of patients with Ambilhar (niridazole). The average prevalence rate of *Schistosoma haematobium* in the population of these two sectors was reduced from 65% in 1968 to 28% in 1970 (McCullough & Eyakuze, 1972). At the end of the first year of operation there was a fall from over 30% in young children prior to the start of the project, to 14%, while the incidence in nearby untreated areas remained about 30% (WHO, 1973).

3. Projects using Molluscicides and more than one other Measure

a) Venezuela

My visits to the endemic areas in Venezuela in 1962 and 1963 lead me to believe that the schistosomiasis control programme in this country has achieved its goal of reducing transmission and prevalence of the disease. Success has been mainly due to the systematic and determined efforts by its competent personnel, to the application of new developments in every known control measure, to the availability of adequate funds and to the collaboration of several government departments. The campaign against the disease started around 1942, but gradually increased in scope and intensity until 1946, when an «Antibilharzia Section» was established in the Ministry of Health, which, since then, has dealt with the problem on a national scale. The programme has emphasized snail control through the use of molluscicides in addition to engineering measures, sanitary measures and chemotherapy.

Copper sulphate, lime, and then NaPCP were used until 1956, after which

date copper pentachlorophenate was preferred. Bayluscide and Frescon were also later utilized. The mollusciciding programme takes the shape of a military operation. In addition to application of the chemical by drip methods, it is applied to foci of snail concentrations along the banks of the watercourse by means of knapsack sprayers. Usually, 2-3 blanket treatments per year are applied. The stock solution of copper pentachlorophenate is stored in large concrete tanks.

Chemotherapy involved mass treatment with Miracil D, and recently hycanthone. A piped water supply as well as sanitary and laundry facilities have been introduced in some villages, and bridges were installed on some small streams to reduce human-water contacts.

Evaluation of the control programme in Venezuela indicates that about 40% of the foci in the endemic area have been eliminated and about 50% have been confined to easily controllable sites. Fecal examinations of random samples in the endemic area showed a gradual reduction from 14.2% positives for *S. mansoni* in the period 1943-1960 to 8.3% during 1961-1964, 4.8% during 1965-1969 and to 2.8% in 1970 (Ferrer-Faria, 1972).

b) Puerto Rico

In 1953 the Puerto Rico Health Department, with technical assistance from the U.S. Public Health Service laboratory in San Juan, initiated pilot control activities in several areas of Puerto Rico. Control efforts included: mollusciciding with NaPCP and later with other chemicals, draining potential snail habitats, the use of the snail *Marisa cornuarietis* as a possible biological control agent, and limited human chemotherapy. Indices of human infection indicate that the disease has declined on the island during the last two decades. In four pilot control areas,

prevalence of infection was monitored annually between 1953 and 1966 with fecal examinations of 6-year old school children. The assays showed an irregularly progressive decline in prevalence. In Guayama and Arroyo control consisted first in chemical and later both in biological and chemical measures against the snail host, *Biomphalaria glabrata*, in addition to the treatment given to infected persons. Prevalence of the disease declined from a maximum of 20% in Guayama and 8% in Arroyo during 1954, to nil in both areas by 1966. However, the prevalence in an untreated area, Caguas, declined from 11% in 1954 to 0.5% by 1965, though it increased again to 1.2% in 1966 (Jobin et al., 1970).

Cline (1972) has expressed the opinion that while the data reveal a decline in the prevalence of schistosomiasis on Puerto Rico during the past two decades, evidence is lacking that it was a result of the pilot control programmes of 1953-1966. There are reasons to believe that dramatic socio-economic advances in Puerto Rico contributed significantly to the decline.

c) Japan

A long standing control programme in Japan has led not only to a marked decrease in the prevalence of the disease in the country, but also to a reduction in the number of endemic areas.

Five endemic areas of schistosomiasis have long been known in Japan. These are the Kofu, Katayama, Chikugo River, Numazu, and Tone River Basins. The number of cases in these areas increased during and after World War II, but a national control program which started in 1950 had considerably reduced the incidence of the disease 18 years later. A survey in 1970-71 revealed new cases only in the Kofu and Tone River Basins. In the

Kofu Basin, formerly the most heavily infected area, only 36 (0.27%) of 13,500 persons were found positive for *S. japonicum* eggs. In 1956 the snail host, *Oncomelania nosophora*, was prevalent over an area of 18,000 hectares, and the population at risk was 370,000; by 1966, however, the area where the snails were found was reduced to 7,333 hectares and the population at risk numbered only 42,751 (Ijima et al., 1964).

The control program combined the use of molluscicides, drainage of swampy habitats, lining of canals with concrete, sanitation, chemotherapy and legislative action. The molluscicide used in Kofu and Chikugo River Basins was NaPCP between 1953 and 1964. Between 1965 and 1970 Yurimin was applied in the Kofu Basin (Yokogawa, 1972). During this period mollusciciding cost the national and local governments 20,000-30,000 U.S. dollars (\$ 1,000 per ton).

d) Iran

In Iran urinary schistosomiasis is endemic in a single province, Khuzestan, in the south-western part of the country. Infection is limited to 7 foci. The number of infected persons was estimated to be 25,000 to 30,000 mostly living in 175 villages.

Control measures in Khuzestan started in 1964, and although the use of molluscicides and chemotherapy were the two main measures taken, environmental modification of the snail habitats by engineering measures, sanitary facilities and safe water supply were also applied (Dr. Gholam Sahba, Former Director of the project, personal communication). Interruption of transmission was achieved in most areas by molluscicides and elimination of the snail habitats. Copper sulphate and NaPCP were used at first but Bayluscide was later preferred. It was used

to treat 197 habitats up to the end of 1967; *Bulinus truncatus* disappeared in 42 sites after one application and in further habitats after repeated mollusciciding operations. In 1968 127 habitats were also treated (Arfaa et al., 1970). Engineering methods were used to eliminate snail habitats by drainage and filling, 47 small and large swampy areas were completely eliminated, while another 27 were partially eliminated. Infected persons in 156 villages were treated with niridazole (Ambilhar). Prevalence of the disease fell from 10% to 2.1% by the end of 1968.

The administration and operation of the Iranian control programme have been excellent, and there has been an impressive impact of control measures in considerably reducing snail population (near eradication in most habitats), and in reducing the number of infected individuals. It is feared, however, that an increase of infection might occur and may jeopardize the success in control, because of extension of the irrigated area by some 130,000 acres.

Future of Snail Control by use of Molluscicides

It is the general consensus that, because of the advanced scientific development of molluscicides, the use of these chemicals in the control of schistosomiasis is an effective technique. The use of molluscicides exerts a marked impact on the prevalence of the disease when applied alone, or when used in integrated control programmes, and it seems that these will be the measure of choice in the foreseeable future. But to obtain even better results with molluscicides, in order to more easily and effectively achieve the goal of the control programme, further advances need to be made regarding the chemical composition of molluscicides, their formulation and methods of appli-

cation, and in the general field of chemical control of the snail hosts.

Although we have at present available certain molluscicides which meet many of the criteria for an ideal molluscicide, we should yet be on the look-out for even better chemicals. Moreover, although new effective formulations of the present molluscicides have been developed we should also look for even better formulations, allowing reduction in costs, in manpower and equipment. Screening and evaluation of molluscicides should be continued. The industry should be encouraged to continue the valuable role which it has played in the past. However, I feel that the industry should collaborate even more by reducing the price of their products. It would be to the advantage of the industry to follow this recommendation so that their products, and chemical control in general, should appeal to countries where the disease is endemic. Public health administrators are always interested, and rightly so, in the cost/benefit analysis of any proposed control programme.

In striving for advancement in the field of molluscicides attention should be given to chemical composition which would result in selective properties; also to methods of application, dispersal, distribution, and dilution of the chemical downstream from the point of application, and to alleviating its side-effects. In all these research endeavours a close liaison should be maintained with other groups interested in the field of pesticides. The necessity for closer coordination of efforts became apparent to me when, in September 1974, I attended a Symposium in Akron, Ohio, U.S.A. on «Controlled Release Pesticides». To my knowledge this is one of the few symposia, if not the only one, in which molluscicide users have taken part. Considerable time and efforts

in molluscicide research can be saved by conferring with workers on other pesticides. Knowledge of the previous experiences of pesticide workers will result in taking a short road to the development of a better molluscicide, to easier and more effective methods of application and dispersion of the chemical and to an understanding of the physico-chemical characteristics of freshwaters which affect the stability and performance of the compound, as well as of the nature and extent of the impact on the environment. Coordinated efforts with specialists in other disciplines of pesticide research will no doubt also result in developing a molluscicide with multipurpose uses, i.e., one that can also be used as an insect larvicide, for example, against mosquito larvae and blackfly (*Simulium*) larvae, and that also would be effective on cyclops, the invertebrate host of the Guinea worm (*Dracunculus medinensis*). Although there are at present such compounds, the carbamates, there is always a need for improvements and advances. Blackflies, whose larvae are aquatic, are the vectors of onchocerciasis (caused by *Onchocerca volvulus*), and the disease occurs together with schistosomiasis in several countries of West and Central Africa. Guinea worm infections are prevalent, together with schistosomiasis, in many African and Middle Eastern countries. The nematode *Dracunculus medinensis* requires freshwater cyclops for the development of its larval stage.

More information is needed with regard to the physiological and biochemical processes in the snail hosts. Some attention was given to these aspects in the early 1950ies, but since then there has been a lag in the data accumulating on the subject. A clarification of the

physiology and biochemistry of the snail hosts will help to a better understanding of the mode of action of molluscicides on these mollusks, and accordingly will help in reaching the ultimate goal of developing an effective and a selective compound. This applies not only to the discovery of new compounds but also to modifying the structure of present molluscicides to make them more selective.

Since the time when copper sulphate was discovered to have molluscicidal properties no one ever doubted the effectiveness of the cupric ion, in spite of the fact that copper sulphate has disappointed many workers. The compound is seriously affected by physico-chemical conditions in the waterbody. It is felt that organo-copper compounds, would have advantages in that it would protect the cupric ion and thus overcome the disadvantages of copper sulphate (Malek, 1974 ; Duncan, 1974 ; Paulini, 1974). Cheng & Sullivan (1974) have theorized that sorption and precipitation of the copper ion may be prevented by its stereo-chemical encapsulation by chelating agents. Cu (DEG)_2^* has molluscicidal properties identical to those of the cupric ion, and might be a development in the correct direction. Other organo-copper compounds should be screened and evaluated.

Only very few field studies were conducted recently on slow-release methods in applying molluscicides, and more attention should be given to this technology. There are still gaps in our knowledge of the suitability of these methods to certain habitats, of the dissemination rates of the chemicals from the matrix, of the effect of environmental conditions, especially silt, in interfering with the release of the chemicals, and of the effect of this

* DEG = N,N-dihydroxy ethyl glycine.

prolonged, or continuous method of application on the environment. Nevertheless, the few laboratory and field evaluations of the method warrant its further use, and its recommendation, to countries where schistosomiasis is endemic. Ritchie et al. (1974) reported that Bis (tri-n-butyltin) oxide (TBTO) formulated in rubber for slow release allows a multimeasure attack against schistosomiasis, including damage to snail oviposition, egg development and hatching, cercarial and miracidial infectivity, and against the most vulnerable age of hatched snails. According to the above authors a range of 1-10 parts per billion of TBTO was effective against the snail and the parasite.

It is necessary to investigate the fate of the slow-release formulations, and accordingly of the chemical, after they are thrown into the water in habitats with soft mud on the bottom, such as occur in many irrigation canals and in some natural streams.

Improved methods of application of slow-release molluscicides are needed. The writer believes that slow-release molluscidal pellets sink in the mud bottom of certain snail habitats, and thus become ineffective, when introduced (applied) by the present methods. He will test his hypothesis this summer in an endemic area in Brazil. Certain habitats with soft mud bottom will be chosen, and the rubber pellets (with TBTO) will be thrown in according to the present application methods. An alternative method will be used in other habitats, with the pellets placed in a perforated (mesh) basket suspended below the water surface, half-way to the bottom. The efficacy of the above two methods in controlling the planorbid snail hosts of schistosomiasis will be compared and evaluated.

Application methods of molluscicides to irrigation schemes and to natural streams still need further improvements.

In Egypt the huge size of the irrigated areas to be treated makes it uneconomical to apply blanket treatments and the only feasible method proved to be focal control (with CuSO_4), i.e., control within a certain radius of inhabited places. This method is known in Egypt as «radial» control.

Blanket application (of Bayluscide), followed by focal application based on surveillance, is followed in Rhodesia. In the Gezira irrigated area of the Sudan, copper sulphate has been used for the last 20 years. At present, however, trials are conducted to compare the efficacy of copper sulphate to that of Frescon. In the Gezira, copper sulphate is used as an initial application at 30 ppm, followed by a continuous application (a maintenance dose) of 0.125 ppm. When the method was evaluated in Kenya it was found effective (Teesdale et al., 1961), whereas when it was evaluated under Sudanese conditions in pump schemes near Khartoum it was found ineffective, mainly because of the poor downstream carriage of the chemical (Malek, 1962a). Nevertheless I concluded that the concept of continuous or prolonged application at very low concentrations is sound and economical if molluscicides other than copper sulphate are used. Irrigation systems can be treated from a single application point at the headwaters and thus liquid (emulsifiable) concentrates can be released effectively for prolonged applications. This has been found to be an effective method in the Arusha-Chini plantation in Tanzania (Crossland, 1967 ; Fenwick & Jorgensen, 1972).

The writer recommends that booster doses should be applied at points further downstream from the intake of canals be-

cause the canals usually support large colonies of snails. The use of such boosters in irrigation schemes needs to be evaluated. Also to be evaluated are solid formulations, in rubber or other matrices, for slow-release in irrigation canals, and in natural habitats. These methods presumably could be more economical and more practical; they may be applied by unskilled personnel without handling risk. Their impact on the environment remains to be investigated.

There is a need to screen and evaluate more molluscicides of plant origin. The possibility exists that they might exert a minimal effect on the environment. Moreover, if not occurring naturally in a country, these plants can be imported and grown on a large scale. The concept is not new; planting of such shrubs and trees along water bodies has been suggested in Egypt and the Sudan more than 40 years ago.

The development of a selective molluscicide should always be the goal in looking for an ideal compound. It should destroy the snail hosts at low concentrations, and at the same time have minimal effects on other members of the biota.

To determine the impact of molluscicides on the biota there is a great need for developing methods to be used correctly and with accuracy, and a need for new and more critical standards of evaluation. Every member of the snail's associate biota should be considered, and the effect of molluscicides dealt with independently in each case. This is to be followed by a consideration of the collective effect on the biota, with particular emphasis on the effect of physical and chemical factors on the impact of molluscicides. In this context, it is not satisfactory if only occasional and crude assessments are made of the impact of molluscicides, nor when laboratory or field evaluations

are conducted alone. Rather, a coordination should be made of laboratory, semi-field, and field testing.

When testing and evaluation is undertaken in the natural habitat the conclusions as to «no effect», or «little effect», or that the microflora and microfauna have been restored to normal conditions should be based on a thorough quantitative survey of each member of the biota, as well as of the hydrography of the area. It is possible in certain freshwater bodies that the biota is restored to normal, because of water flowing into the water course from some affluents, or from some protected pockets along the banks which the molluscicide did not reach or did not affect.

The failure of certain mollusciciding operations may be only due to the lack of trained personnel in charge of molluscicide application, especially at the technician level. International Organizations and fund-giving agencies can alleviate this shortage by establishing one or more schistosomiasis control training centers, in one or more centrally-located developing countries. During my services for the World Health Organization I have made similar recommendations to WHO, and on several occasions, to the UNDP. I consider that such training, i.e. at the technician level, at such centers, is more important and more urgent than academic training at universities, which some schistosomologists still advocate and to which they still give priority.

Integrated Control Measures

For the control of schistosomiasis, chemotherapy, environmental sanitation, snail control, and control of human water contacts are the recognized control measures. Because transmission of the disease shows a varying picture from one endemic area to the other, on account of biolo-

gical and ecological variation, each control measure could prove either very effective, or less so, according to local conditions.

In recent years more data indicating the public health significance of schistosomiasis *mansoni* and schistosomiasis *japonica* have been presented. The attitude even of many investigators and public health authorities has changed with regard to urinary schistosomiasis. From findings in the last decade it is now recognized that attention should be given to the important consequences of urinary schistosomiasis.

Although convincing evidence has been presented in this paper of the effectiveness of chemical control of the snail hosts, and thus of reducing transmission, it is often difficult to convince public health officials to embark on an expensive programme in the use of molluscicides, especially when other diseases may have greater priority. The officials are generally reluctant to adopt control programmes from lack of confidence in the success of the control measures and also because of the uncertainty of their costs. However, many of us who have used molluscicides in field operations are convinced that there is every reason to believe that molluscicides will continue to play a major part in the control of schistosomiasis, as a single measure in several situations, or in the combined control of this disease.

It is recognized that socio-economic standards must be elevated first before sanitary measures will be accepted by the population. Thus it is logical and practical to adhere to other control measures, while, in the meantime, continuing with a certain degree of improvement of sanitary conditions.

Environmental control measures have the objectives of making the snail habitats untenable or less suitable for the snail hosts, and to prevent or reduce human contacts with potential transmission sites. Those environmental measures which involve the provision of water supply schemes to the community, even in the form of a few public faucets, will prevent people from going to streams where they are exposed to the infection.

If we consider snail control we find that a consideration should be given to both chemical and environmental measures. Several control projects, where environmental measures have been used alone, or in combination with molluscicides, have been ably reviewed by Buzo (1972), and several such engineering methods have earlier been contributed by him to several WHO publications (WHO, 1965b, 1968b). The selection of the control method or methods must depend on an assessment of local conditions, and the cost of the control measures. In some situations drainage, filling, water management, or modification of agricultural practices would reduce or eliminate snail populations. In most areas effective control at reasonable cost can be obtained only by a combination of methods, i.e. modification of the habitat and then application of molluscicides to the remaining colonies. The two snail control measures supplement each other in many situations.

A certain degree of effective schistosomiasis control, obtained through the two combined measures of snail control is financially feasible and accordingly appealing to authorities. Other environmental measures designed to reduce or eliminate contact with water might be equivalent to snail control. Implementation of control measures against schistosomiasis, even if they require a high initial

capital funding, are acceptable to health authorities and to the local community, because they usually serve a variety of health purposes, i.e. control several other diseases.

For example, environmental measures, in addition to controlling snails and human-water contacts can eliminate the breeding sites of mosquitoes and other insects and arthropods, as well as water-

filth diseases; molluscicides could kill snails, mosquito and blackfly larvae and cyclops. Thus it is evident that for a better and a hopeful future of schistosomiasis control, the programmes should be integrated into the regular health services in so far as possible. Such integration will also have the added advantage of ensuring financial support of control, and promoting a better coordination of activities.

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COST-BENEFIT ANALYSIS OF THE USE OF MOLLUSCICIDES IN DIFFERENT ENDEMIC AREAS

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The problem faced by the government in an area where schistosomiasis is endemic is to decide what priority should be given to its control and what amount of money should be allocated for that purpose. Since several control methods have been advocated alone or in combination, the decision process becomes more complex. Cost-benefit analysis may help the administrators to decide on alternative courses of action.

In the present paper we limit our consideration to the use of molluscicides as a sole control measure. This limitation is, however not equivalent to saying that molluscicide is the first choice among the control techniques. We shall use the case of molluscicide only as an example to indicate the line of reasoning. The same reasoning may be used for other control techniques by introducing the necessary alterations in figures and factors.

In order to carry out the cost-benefit analysis we have to define the costs and the benefits of a control campaign then to establish relationship between :

- a) disease and infection,
- b) infection and environmental conditions,
- c) environmental conditions and molluscicide application.

What are the costs of a molluscicide control campaign ?

Usually the costs are the expenditures made during and in relation with a control campaign. The main components of these expenditures are : chemicals, dispensable materials, equipment, vehicles with depreciation, fuel, maintenance, labour, rent, administrative running expenses (over-head), surveys, supervision, consultants, fees, daily allowances, etc. In a broader sense, however, costs are more than simple expenditures of money. The money spent on a snail control campaign might have been spent on a mobile X-ray unit which could have detected a certain number of new cases. Early detection might have prevented a certain number of early deaths due to TBC. It is reasonable, therefore, that the costs of the undetected cases, in this example, be added to the costs of the snail control campaign. In an analogous way, the personnel employed in the snail campaign might have been used for the expansion of the malaria campaign or for a small-pox eradication program. The cost of the opportunity of employing the human resources in an other program should be charged also to the debit account of the snail control campaign.

According to this reasoning the analysis of the costs require much more

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study than the simple summation of money to be spent on materials, equipment, labour, transportation and supervision of a campaign.

What is the benefit of schistosomiasis control ?

The immediate and subjective result of an improvement in the health situation is that people feel better. It is not necessary that they should work more or earn more. As a matter of fact a few studies on the economical effect of the presence of schistosomiasis reported from Tanganyika, Cameroon and St. Lucia failed to show any influence on the productivity of workers.

Cummins (1972) analysing the economical implications of schistosomiasis and the apparently conflicting results obtained and reported in those few studies mentioned above raised the hypothesis that :

- i) Either the areas studied show different severity of the disease or the economical behaviour of the populations investigated is different ;
- ii) The kinds of effects produced by the disease are different from those investigated and a different sort of investigation would be necessary to find them.

The Public Health authorities may tend to view the problem of schistosomiasis in proportion to the measurable impact of the disease on the physical well-being of the population. Even this task is difficult as demonstrated in the Report of the Scientific Group (WHO, 1967) where it was noted that the investigations carried out in different regions showed always great differences but, due to different methodologies employed, it was impossible to separate the subjective

variations from the epidemiological differences.

The same Group has stated that mortality, morbidity and disability are the criteria employed for evaluating the sanitary or social importance of a disease but the importance of these factors in any economic system depends :

- i) on the value given to the temporary or permanent losses caused by incapacity or by death,
- ii) on the direct burden caused by medical care, and
- iii) on the indirect losses caused when individuals become economically dependent.

However, the official concept of health established by WHO is much more than the usual criteria of death, disease and disability, and takes into consideration social well-being as well.

Paulini (1974) suggested that the reduction of the number of worms in a human population is a useful indicator of the benefits gained by a control campaign ; assuming that the greater is the reduction of endemicity the greater is the benefit.

The Worm Population Model

The transmission of schistosomiasis may be expressed by a change in the number of worms over a unit time and the endemicity of the parasitism will be given by the total number of worms, at a certain moment, in the definitive hosts.

If (in the several subsequent models) we denote with

- n — the number of female (paired) worms in a human community,
- X — the daily cercarial density in the transmission foci (cercariae/m³),

h — the daily man-hour contact with the transmission foci ;

m — the rate of mortality of female (paired) worms,

s — the survival rate of the same worms ($s = 1 - m$)

z — the infectivity of cercariae

i, j — number of years

then it can be shown (see Transmission Model in Annex) that the probable number of worms acquired by a community under given epidemiological conditions over a certain time period can be expressed by (1),

$$n_i = (T/m) (1 - s^i) \quad (1)$$

where T is the transmission function defined by (2), where the summation is extended over one year, and its value is considered constant over i years.

$$T = z \cdot \sum h \cdot X \quad (2)$$

From (1) it follows that when i increases, n will tend to a limiting value which is

$$\lim_{i \rightarrow \infty} n = \frac{T}{m}$$

Also the rate of transmission is defined by

$$dn/dt = T$$

The endemicity (N) is given by the sum of the worms in the human population :

$$N = \sum n_y = y \cdot \bar{n}$$

where y is the number of individuals and \bar{n} is the mean number of worms per individual.

Figure 1 shows the build-up of worm populations in 30 years with different values of transmission-functions (T) ; the

rate of mortality of female worms (m) was taken as 0.1 per year.

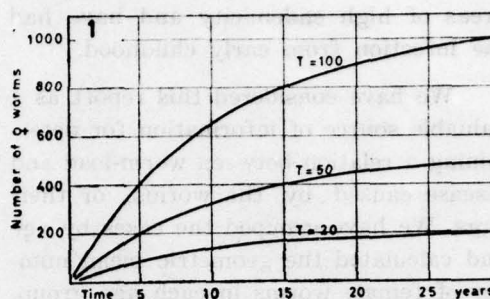


Fig. 1. — Build-up of worm-burden at different level of transmission (T).

The Disease Model

In order to express schistosomiasis as a disease in numerical terms one has to find a relationship between the clinical symptoms and intensity of infection. According to Scott (1960) «the theoretical value of an estimate of intensity lies in being able to correlate the number of worms harbored with the severity of effects of infection». The same author recognized two problems involved in applying this idea to schistosomiasis : the first was whether egg counts give a reliable estimate of the intensity of infection ; the second was whether any relation exists between worm burden and clinical symptoms.

For the first question the studies of Cheever (1970), among others, gave an affirmative answer when he reported 10-20 eggs per gram of stool per pair of worms in light or heavy infections without Symmers fibrosis.

For the second question the studies of Carvalho Luz (1970) might provide an answer. This author reported on 136 cases of portal hypertension due to schistosomiasis. During splenectomy the

worms were removed through extraorporeal filtration of the blood and were then counted. The patients came from areas of high endemicity and have had the infection from early childhood.

We have considered this report as a valuable source of information for determining a relation between worm-load and disease caused by the worms, or their eggs. We have grouped the cases by age and calculated the geometric mean number of female worms in each age group. The results are shown in Table 1.

TABLE 1. Variation of the mean number of female worms with the age of patients

Age group years	Number of cases	Number of female worms (geometric mean)
8-10	13	393
11-13	14	341
14-17	15	353
18-22	26	273
23-29	20	176
30-39	20	164
40-49	11	144

Visual observation of these data suggests a negative correlation between age and mean number of female worms which led to that stage of disease.

We have multiplied the mean number of female worms with the central value of the age-group and obtained relatively constant values (Table 2).

TABLE 2

Age group	Age \times mean No. of worms (worm-years)
8-10	6540 corrected for weight
12-13	5600 " " "
14-17	5480 " " "
18-22	5460 " " "
23-29	4760 " " "
30-39	5740 " " "
40-49	6200 " " "

The value of time \times load = constant effect is similar to the well known relationship observed in toxicology, pharmacology, insecticide and molluscicide-testing as well as in industrial hygiene.

Concentration \times exposure time = C^n where $n = 1$, $C = \text{constant}$.

A similar relation was also found in the investigations on the effect of smoking. In all of these instances the biological response is dependent both on the quantity (concentration) of the agent and on the duration of action.

These analogies suggest that certain pathological manifestations of schistosomiasis become highly probable when the infected individuals have experienced a given dose measured in worm-years (dose = Number of female worms \times period of infection).

It is impossible to tell, at the time of the splenectomy (when the worm-burden is verified) what was the rate of acquisition and of loss of worms by that person during the previous 10, 20 or 30 years. For illustrative purposes the formation of three different worm-burdens is given in schematic form in Fig. 2. The first case is represented by a constant

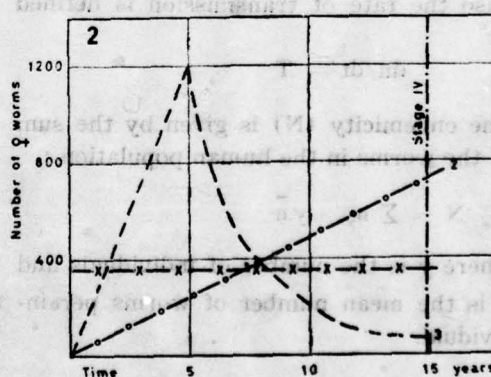


Fig. 2. Three possible courses for the establishment of worm-burden at Stage IV of schistosomiasis, i.e. the stage of critical irreversible hepatosplenomegaly (simplified).

number (380) of female worms over 15 years; the second one shows a linear increase up to 740 during the same period; the third one represents a few massive infections (1200) followed by a gradual loss of worms (down to 80). It should be noted that the dose (worm-years) is identical for all the three cases but the number of ♀ worms at the time of recovery varies from 80 to 740. It is reasonable to expect that all three cases and their combinations may occur in an endemic area.

If we accept that the dose in worm-years determines the irreversible alterations caused by the infection we may proceed to an analysis of the consequences which result from different degrees of transmission in an area endemic for schistosomiasis. For this purpose Fig. 3

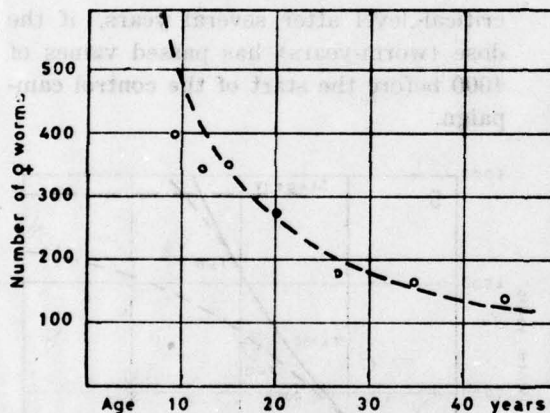


Fig. 3. — Relation between the geometric mean number of female worms and the age of patients with portal hypertension (stage IV schistosomiasis mansoni)

was drawn. It shows the constant-effect line in the coordinates: No. of female worms and age of the individuals. The circles are the observed values taken from Table 2. The equation of the line is

$$5680 = \text{♀ WORMS} \times \text{AGE}$$

The interpretation of Fig. 3 is quite straightforward: The area to the left and

below the curve represents all those infected persons who harbor parasites for a given number of years; in these the average number of parasites multiplied by the duration of infection has not reached the critical value for irreversible hepatosplenomegaly combined with hypertension (i.e., Stage IV in schistosomiasis mansoni).

We have then calculated the dose in worm-years, at different transmission levels. The results are shown in Fig. 4. At high transmission rates the critical level (Stage IV) may be reached in less than 10 years. At low transmission rates the critical level may not be reached within a life-time.

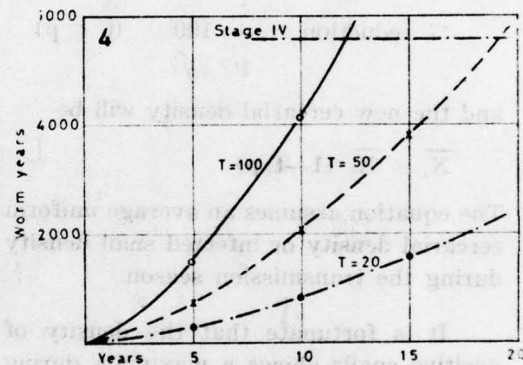


Fig. 4. — Increase in the dose in worm-years at different levels of transmission (T).

The dose (worm-years) can be expressed in analytical form

$$\text{Dose} = T \cdot \frac{P}{2} \cdot i S^{p-1} + T \cdot \frac{1}{2} \cdot \frac{1}{(1-S)} \quad (3)$$

where p = length of transmission period

The Molluscicide Control Model

Let us suppose that one treatment with molluscicide eliminates all infected

snails from a transmission-site which then remains free of infected snails for about one month (5 weeks). If transmission occurs the year around, for 12 months, then one treatment with molluscicide will represent the average reduction of $1/12 = 0.083$ ($= 8.3\%$) in cercarial density and probably an equal, 8.3% , reduction in the number of new worms acquired during that year.

If we denote by t the number of molluscicide applications per transmission season and p is the length of the transmission season in months, then the average yearly reduction in cercarial density and in the probable number of worms will be

$$\% \text{ reduction} = -\frac{t}{p} \cdot 100 \quad (t < p)$$

and the new cercarial density will be

$$\bar{X}_1 = \bar{X}_0 (1 - t/p)$$

The equation assumes an average uniform cercarial density or infected snail density during the transmission season.

It is fortunate that the density of positive snails shows a maximum during some months in many endemic areas and then declines. Treatment with molluscicides in the period of peak cercaria production will produce greater reduction in cercarial density than that indicated by the equation.

If the transmission has been interrupted by the application of molluscicide for a number of years (j) starting at year (i), then the number of worms which existed at the start of the campaign will decline exponentially according to

$$n_j = s^j (T/m) \cdot (1-s^i) \quad (4)$$

If the transmission is not completely interrupted, then the above equation re-

ceives an additional term, which will lead to a new, lower level of endemicity,

$$n_j = s^j (T_i/m) \cdot (1-s^i) + (T_j/m) \cdot (1-s^j) \quad (5)$$

with the following rate of loss of worms :

$$dn/dt = (s^{j+1} - s^j) [(T_i/m) (1-s^i) - (T_j/m)] \quad (6)$$

The disease model with snail control

When the transmission of schistosomiasis is greatly reduced or interrupted by molluscicide treatment for a number of years, then the worm-load of the infected person will start to decrease, due to the natural death of worms. The dose, expressed in worm-years, however, will continue to increase, although at a slower rate. The influence of interruption of transmission on the dose is shown in Fig. 5 where the dotted lines, at high rates of transmission may still reach the critical level after several years, if the dose (worm-years) has passed values of 4000 before the start of the control campaign.

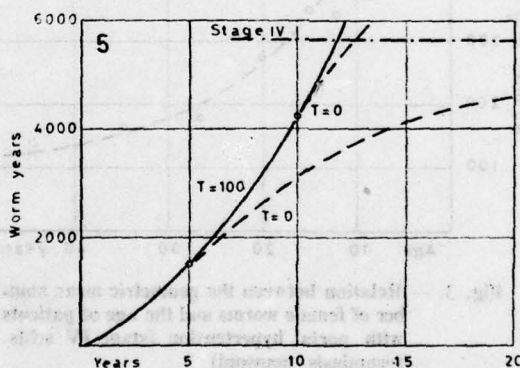


Fig. 5. Influence of the interruption of transmission (T) on the build-up of dose in worm-years in an area of intense transmission.

At lower rates of transmission the control campaign will, probably, not permit anybody to reach the critical level. The same may be also true for those persons who had accumulated a dose of

only 2000 worm-years when transmission has been interrupted in areas of intense transmission.

The snail control campaign will separate the population of a highly endemic area into two distinct groups: a small one, which will develop the severe form of the disease even in the absence of transmission, and the larger second one which might be cured by the spontaneous death of the worms, without suffering from the sequelae of the disease.

In areas of low endemicity, the reduction or interruption of transmission will reduce the worm-burden of the infected persons to a low level. At this level the development of severe forms of the disease might be impossible even with very long-standing infections.

Costs (expenses) of mollusciciding operation

We may distinguish three types of transmission sites in the areas where schistosomiasis is endemic: small ponds, streams, and lakes. These three types of snail habitats may require different techniques of molluscicide-treatment.

In small ponds, the molluscicide to be applied is calculated according to the volume of water, therefore the costs increase with the volume.

In streams, the molluscicide to be applied will depend not only on the flow-rate of the stream, but also on the effective length of molluscicidal activity. Therefore the costs will be proportional to the quotient: (volume of water treated in m^3 /effective length in kilometers).

In lakes, the application of slow release formulation deposited on the bottom may be effective (Magendantz, 1974). The application is calculated in grams of

active ingredient per hectare of area. It should be mentioned that under some conditions transmission sites of a big lake can be isolated from the main water-body and can be treated with molluscicide as a small pond.

In order to bring the different types of application to a common denominator we divide them by the number of population protected, arriving at the general formula:

$$\text{cost/capita} = \frac{(\text{unit cost}) \times (\text{number of applications per year}) \times \frac{\text{water unit treated}}{\text{population protected}}}{\text{population protected}}$$

Water units are: m^3 in ponds, m^3/km in streams, hectares in lakes.

It is also understood that in estimating the unit costs due consideration is given to the cost elements (surveys, administration, supervision, etc.) which are not directly related with the molluscicide application.

The Value of Schistosomiasis Prevention

We have to estimate the benefits of a schistosomiasis control campaign in monetary terms, in order to compare them with the costs of the campaign. Several methods have been developed to make some estimate of those benefits which are not usually considered in monetary units.

One method of valuing improvement of living or working conditions which leads to disease control is the «alternative cost» procedure. As the name indicates the improvement meets a need which may be satisfied by different means and for different prices. If the improvement was achieved for the lowest price,

then a saving was obtained which is the difference between the highest and lowest bids. This saving is then considered as the value of the improvement.

Another method is employed in the area of prevention of accidents. The standard procedure is to calculate the loss of income plus the medical care including medicine and then to consider this value as first approximation to the correct one.

Neither of the two methods mentioned seemed to offer us a wide enough range of applicability and, at the same time, simplicity, for our present purpose.

However, following the idea of Schelling, cited by Lave & Weber (1970), we can argue that freedom from schistosomiasis may be obtained by a control service which can be purchased by customers in the same way as other services. According to this idea, the individuals demand for health can be used for expressing their monetary evaluation of the reduction in the probability of becoming infected and/or diseased by schistosomes.

There is no evidence on what individuals would be willing to pay for avoiding schistosomiasis. Inquiry among the population would be of little use because of some major difficulties:

i) An individual should have a clear idea of the outcome of infection in order to decide on alternative courses of action; this condition is usually not fulfilled. It is doubtful whether the majority of any human population is able to judge a course of future events which have low probability;

ii) Individuals living in highly endemic areas usually have a low level of income which may be barely enough for the food supply of the family and for the minimum of clothing. There is nothing or

almost nothing left for medical care or medicines in case of sickness;

iii) The income may be in «kinds» and is therefore not exchangeable;

iv) Control service may not be available.

We propose therefore, that the concept of individuals' demand for health should be replaced by the government's demand for health. We argue that (i) the governments (local, state or federal) are responsible for the health of the communities; (ii) individuals, or small communities, may not have resources for carrying out preventive action against schistosomiasis; (iii) individuals or small communities may not have the capacity to decide on what course of action they should take.

We should investigate now what a government would be willing to pay to decrease the probability of people becoming infected or diseased by schistosomiasis; in other words, what is the government's demand for health.

At this point we have alternatives: either we make calculated guesses on the government's demand for health, where the guesses might be both unrealistic and impolite — or we try to infer what the government's demand would have to be in order to justify a control campaign. A government then can make use of these estimates in making the decision.

The dollar benefit Z per person which the government would receive from a control campaign is calculated according to equation:

$$Z = B \cdot D \cdot A \cdot w$$

where B is a scalar which characterizes the government's demand for health; D is the present discounted value of the money spent over i years with r rate of interest,

$$D = \sum_{i=1}^i 1/(1+r)^i$$

A is the reduction factor of the disease or of transmission by a given control technique ; **w** is the relative weight which the government places on a certain type of control.

We note that **i** can be selected at will; we shall use 10 years as a reasonable time horizon. We shall use 6% for the discount rate but admit that government may use different discount rates in their estimates.

If we take **Z** as the cost of snail control the government is willing to bear, expecting to receive an equal or higher benefit by the reduction of the endemicity of schistosomiasis, then the government's demand for health (**B**) can be estimated by

$$B = Z/D \cdot A$$

For example, if we spend \$1 per capita per year for 10 years, on a molluscicide campaign, which will reduce the yearly rate of transmission by 90%, then we may calculate the new endemicity by the formula (5)

$$N_j = s^j (T_j/m) (1-s^i) + (T_j/m) (1-s^j)$$

The reduction of endemicity is

$$\frac{N_i - N_j}{N_i} = 1 - \frac{N_j}{N_i} = 1 - \left[s^j + (T_j/T_i) \left(\frac{1 - s^j}{1 - s^i} \right) \right]$$

Taking $j = i = 10$; $s = 0.9$; $T_j/T_i = 0.1$ and solving the equation,

we can expect a reduction of 0.551 in endemicity, or 55.1%.

The aggregate value (**Z/D**) of \$10.00 spent over 10 years is \$13.97, taking 6% for the annual rate of interest ;

then

$$B = 13.97/0.551 = \$ 25.35$$

The government's demand for health for the inhabitants of the endemic area may be more than \$26 per person. In this event, the control campaign brings more benefit than the money spent on control.

If the government's demand for health is only \$15.00 per person, then the campaign may be considered too expensive and either cheaper techniques should be used or the schistosomiasis program should be postponed until the «demand for health» will have reached the estimated cost figures of the control campaign.

For those who prefer to use the rate of prevalence instead of endemicity we give two examples of calculation.

1. Snail control with application of Baylucide (Niclosamide) was practiced during 3 years (1966-69) in Belo Horizonte at an estimated per capita cost of \$0.50 (Paulini & Dias, 1971). A reduction in infected snails of more than 90% was observed. The rate of prevalence in schoolchildren dropped from 28% to 16%.

$$B = 1.68/0.12 = \$ 14.06$$

2. Application of Frescon for 5 days at intervals of 7 weeks has been reported from Tanzania at an annual cost of about \$4400 or \$0.9 per capita per year. According to Webbe (1972) the rate of prevalence dropped from «over 50% to approximately 20% through the use of molluscicides alone», in about 4 years. The calculation gives for demand of health

$$B = \$ 13.91$$

It was impossible to bring an example for the reduction of the disease (severe forms) by the use of molluscicides because we couldn't find suitable data

which could permit the calculation of the demand for health. However we may take a hypothetical situation to illustrate the cost-benefit estimate for a campaign which has the objective of eliminating the severe cases only.

We assume that the rate of prevalence of severe cases (Stage IV) is 10% in a certain area. Molluscicide application is planned for 10 years at a yearly cost of \$ 1 per capita which will bring the rate of prevalence down to 2%.

The government's demand for health, in this campaign will be

$$B = \$ 174.64$$

From these examples it becomes evident that the demand for health shows low values when the improvement in the health indicator is high, when it can be brought about in a short time and the cost of control is moderate. When the improvement in the health indicator (endemicity) becomes less and less with the progress of the control campaign, the demand for health will increase, in the inverse proportion.

Summary and Conclusions

An attempt has been made to develop a mathematical model for estimating the probable endemicity of schistosomiasis mansoni in a community based on a few variables like length of water-contact, cercarial density, and rate of mortality of worms. An empirical model was developed for the severe forms (non-compensated portal hypertension) of the disease too, taking into consideration both the length of time of the infection and the number of paired worms harbored during that same time. These models helped us to make qualitative and some quantitative

forecasts on the changes of endemicity when transmission has been reduced by snail control with molluscicides.

The benefits of a schistosomiasis campaign were attributed to two variables :

(1) To quantitative changes in an indicator which should characterize the endemic situation (indicators may be the rate of prevalence, the number of paired worms, etc.) ;

(2) To the «demand for health», which expresses in monetary units the value of a service which reduces the rate of prevalence and protects the individuals from becoming parasitized.

It is recognized that the «demand for health» may vary not only from country to country, but also from area to area within the same country.

The major difficulty in our present analysis was the lack of data, both in the mathematical model and in the estimates of costs. Cost figures were obtained from experimental field studies but not in a routine control service.

The general conclusion which emerges from this study is that schistosomiasis control is amenable to cost/benefit analysis, even in the absence of quantitative data.

The conventional cost-benefit analysis assumes that an individual's demand for health is equivalent to or higher than his loss of earnings due to sickness or to premature death. We have recognized that this concept is valid for individuals in a system of market economy but has questionable validity for population groups living in endemic schistosomiasis area. Therefore it is the government's duty to calculate their own demand for health regarding their subjects.

Economic progress is evident in every country of our world, therefore estimates about the value of health based on the present Gross National Product might be grossly misleading. On the other hand, the present planning methodology may permit the approach of a future «sce-

nario» with a certain degree of probability. The estimates of demand for health then may be made according to the planned future state of the society in which the contribution of a healthy person to the nation will be much more valuable than it is at present.

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ANNEX

Transmission Model of Schistosomiasis

If a waterbody (still-water) of volume V contains a number of cercariae C , then the cercarial density X is

$$X = C/V \text{ (number of cercaria/m}^3 \text{ of water)}$$

If the probability of not-becoming infected during an exposure of 1 hour to the water containing X cercariae per m^3 is $q(X)$, then by definition the probability of becoming infected is

$$p(X) = 1 - q(X) \quad (1)$$

At a new cercarial density ($X + dX$) the probability becomes

$$q(X) + dX = q(X) - q(X) \cdot z \cdot dX \quad (2)$$

where z denotes the infectivity of cercariae. After regrouping and integration we obtain

$$q(X) = \exp(-z \cdot X) \quad (3)$$

under the condition that $q(0) = 1$.

The equation (3) is the mathematical expression of the probability of a favourable event (not-becoming infected) to occur with increasing cercarial density.

It follows from (1) and (3) that the probability of becoming infected by at least one female worm is

$$p(X) = 1 - \exp(-z^1 \cdot X) \quad (4)$$

at a cercarial density of X and infectivity $z^1 = z/2$

If $p(X) \leq 0.1$ then (4) becomes

$$p(X) = z^1 \cdot X \quad (5)$$

If the human contact with infective waters is expressed in man-hours (h), then the probable number of worms acquired will be proportional to the time of contact

$$n = h \cdot p(X) \quad (6) \text{ and}$$

substituting (5) into (6)

$$n = h \cdot X \cdot z^1 \quad (7)$$

In m days the probable number of acquired female worms will be

$$n_m = z^1 [h_1 \cdot X_1 + h_2 \cdot X_2 + \dots] \\ h_m \cdot X_m] = z^1 \sum_1^m h \cdot X \quad (8)$$

If (8) covers the time-span of one year, we may consider it as a characteristic of the transmission-site which may remain fairly constant, under stable epidemiological conditions.

If we denote the rate of survival of the female worms by s then after one year the probable number of female worms will be

$$n_1 = T \cdot s \quad (9)$$

and after i years

$$n_i = Ts + T \cdot s^2 + \dots Ts^i = T \sum s^i = \\ (T/m) (1 - s^i) \quad (10)$$

THE FAYOUM SCHISTOSOMIASIS CONTROL PROJECT, AN INTERIM EVALUATION

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Earlier field trials carried out in Tanzania, South Africa, Rhodesia and Egypt have proved that Bayluscide is one of the more reliable molluscicides. It was considered to be the molluscicide of choice in most of the snail habitats encountered in Egypt (WHO, 1965).

In 1966, a large scale trial of this compound was organised by the Ministry of Health in Fayoum Governorate. The amount of Bayluscide to be used in the initial phase of the project and the equipment necessary for its application were supplied by courtesy of the Federal Republic of Germany and the manufacturers of the compound (Farbenfabriken Bayer A.G.).

The plan of action included treatment of the infected individuals. Adult patients were to be given the «standard» course of tartar emetic applied in Endemic Diseases Hospitals all over the country, while children and adolescents were to be treated with Niridazole (Ambilhar, Ciba-Geigy). This chemotherapeutic agent has previously proved its efficacy and safety, particularly when used for treatment of the younger age groups infected with *Schistosoma haematobium* (Abdallah & Saif, 1969), which is the only species of schistosome prevalent in the Fayoum. The Swiss Government has kindly donated 100,000 courses of treatment of Ambilhar tablets.

The Fayoum was chosen because it is a self-contained irrigation unit supplied by a single feeding canal, the Bahr Youssef, which takes from the Nile. Its length is 300 km before entering the Fayoum. It runs through four Governorates in Upper Egypt and only the last 25 km are within the boundaries of the Fayoum.

The Fayoum has a population of approximately 1,100,000 people living on a surface area of 400,000 Feddans (1 Feddan = 4,000 m²). The governorate is serviced by 40,000 km of irrigation and drainage channels, with a water volume of 8 million m³.

In 1968 a total coverage survey was made in the Fayoum to obtain base-line data for future work. The overall prevalence rate for schistosomiasis haematobia in a sample of over 1/5 of the total population (261,606 inhabitants examined) amounted to 45.7%. Of the stream lengths 18.4% were found infested with *Bulinus truncatus*.

The campaign started in 1969; 93 rural health units, 11 urban health centres, and 150 snail control units and centres were involved in the execution of the control measures. During the initial phase of the project (1969-1971), mollusciciding operations involved two blanket applications of Bayluscide every year. The maintenance phase started in 1972 and is still continuing. During both phases the me-

thodology of application of the molluscicide, the concentrations used and the timing of the operations were all subjected to modifications according to the experience gained and to the results of the systemic snail surveys carried out as detailed in the plan of action.

The results obtained clearly demonstrate the impact of combined snail control and treatment of infected individuals in Fayoum Governorate over a period of 7 years. Comparable samples of the population were examined yearly, and a progressive drop in the prevalence of *Schistosoma haematobium* infection was consistently recorded. Among 329,501 individuals examined in 1974 only 9.1% were found infected, while during the first half of 1975 an infection rate of 8.1% was found among 157,344 persons examined.

In 1971 a survey was carried out in 64 villages among children aged 0-5 years

in an attempt to investigate the incidence of infection. Among 6,367 children aged 0-2 years not a single case of urinary bilharziasis was detected; while 204 positive cases were recorded among 7,634 children aged 2-5 years (2.6%). In 1975, 8,133 children aged 0-5 years were examined, of whom 14 were passing ova of *Schistosoma haematobium* (0.17%).

The length of canals and drains infected with *Bulinus truncatus* were very significantly decreased by the end of the initial phase of the project, i.e., in 1972 only 0.004% of 37,117 km examined were infested against 18.4% of 39,542 km in the base-line survey.

Fuller detail on this campaign can be found in a working paper presented to a WHO Expert Committee on «Schistosomiasis Control» (Abdallah, 1972) and in a recent monograph (Ministry of Health, 1975), as well as in Technau (1974).

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THE GEZIRA SCHISTOSOMIASIS RESEARCH PROJECT, SUDAN, CONTROL ASPECTS*

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The Gezira irrigation scheme, which lies between the Blue and White Niles, to the South of Khartoum, covers an area of approximately two million acres. Within the whole of the Gezira there has been, over the past 20 years, a serious increase in the endemicity of schistosomiasis mansoni. The general prevalence is 60-75% and in the age group 8-14 years almost every individual is infected; this has been attributed to lack of adequate control measures.

It was against this background of high prevalence and wide distribution of the disease that the Ministry of Health of the Sudan requested the development of an effective procedure for the control of the disease. Towards this end a pilot project was established with the following more immediate objectives.

Objectives

(a) To evaluate the existing snail control measures by copper sulphate and mechanical barriers, and to examine the performance of N-trityl morpholine (Frescon) under the condition of irrigation as practised in the Gezira Scheme, with a view to eventual control of schistosomiasis throughout the Gezira.

(b) To collect sound epidemiological and biological data as a basis for a study of the dynamics of schistosomiasis transmission so that predictions can be made as to the efficacy of control measures.

(c) To assess the public health significance of schistosomiasis under defined conditions of transmission.

(d) To determine the economic significance of schistosomiasis among the industrial and agricultural workers in the Gezira.

(e) To assess and develop more effective parasitological and immunological diagnostic tests.

(f) Training of personnel.

Within the frame-work of this project, an area of 200,000 feddans (1 feddan = 1.038 acres), has been selected for trials on a large scale.

The Irrigation System

Water from Sennar Dam is brought to the trial site by means of gravity through the 204 km long Gezira main canal. From the main canal the water flows into a series of major canals and from these to minor canals. Along the length of each minor canal, at 300 m in-

* The project is financially supported by the Sudan Ministry of Health, the National Council for Research, London School of Tropical Medicine and the Medical Research Council (U.K.). Further support is received from the WHO for the establishment of a Bilharzia Training Centre.

tervals, are situated the offtakes of small irrigation channels, called Abu-Eshreens, running at 90° to the minor. Each Abu-Eshreen carries water to 90 feddans of cropped land. From the Abu-Eshreen the water flows into smaller channels called Abu-Sittas, and from these into the gadwals, channels running parallel to the Abu-Eshreen and onto the crop.

Water flows into the system from Sennar Dam from 15 July to about the end of March. During the remaining interval parts of the system are supplied by pumps from the Blue Nile. This water supplies the villages without wells and is used for the irrigation of gardens. Under normal conditions of irrigation, the water flow in any Abu-Eshreen needs to be maintained 12 hr per day for 7-8 days, and then the Abu-Eshreen is closed for about 7-8 days. One complete cycle of irrigation takes 14-16 days.

Snail distribution in relation to the different water-courses

Bulinus truncatus and *Biomphalaria pfeifferi* are present in all the different water courses. Their numbers are relatively few in the main and the major canals, but are much greater in minor canals and some Abu-Eshreens, where conditions for snail breeding are better. Snails may also be found in Abu-Sittas, but, as these dry out frequently and completely, they do not survive long nor do they breed.

Experimental Work

Re-assessment of the control methods in operation

Comparative field trials were conducted to determine the relative efficacy for snail control of copper sulphate, the molluscicide in use, and N-tritylmorpholine 16.5% emulsifiable concentrate (E.C.)

(Amin, 1972). This trial involved an area of 43,000 feddans treated with Frescon and a comparable area treated with copper sulphate.

As a result of the excellent coverage obtained with N-trityl morpholine as compared with copper sulphate, an area of 120,000 feddans was selected for further applications with a view to recommending an optimum annual regimen for snail control. The objectives of these applications were to determine the :

- A) Frescon concentration required for optimum snail control ;
- B) Length of time of application ;
- C) Best time of the year for applications.

Applications of N-trityl Morpholine to the pilot area

The recommended method of applying N-trityl morpholine to irrigation schemes was to drip feed a low dose of the chemical for long periods so as to obtain a blanket treatment. Initially the chemical was applied at the head of the pilot area on the Gezira main canal. The applications were made under the different conditions experienced at different times of year.

The formulation used was F×28 (a 16.5% E.C.) ; it was applied by means of a constant head Pearson Mark II dispenser (Shell Chemicals, 1974).

During the non-irrigation periods the application was mainly by aircraft.

Methods of Assessment

- (a) Penetration of the system by the chemical front

The drip-feed method of application depends upon the water flow within the

irrigation system to transport the chemical from its single application point to the canals in which the target snails are found. Since the irrigation pattern changed with the time of the year the efficiency of this method might be expected to change also. The rate at which the chemical was spread through the system was therefore checked by a field analytical technique (Beynon & Thomas, 1967). Water samples were taken from various stations in the canal system to determine the time taken for the front to travel to each point in turn.

(b) Coverage of the system with N-trityl morpholine

The arrival of the chemical front throughout the system signalled the start of a second series of analyses to determine whether the molluscicide was still present in lethal concentrations. N-trityl morpholine hydrolyses in water in a first order reaction dependent upon pH.

Water samples were again collected, this time from the tail ends of minor canals where N-trityl morpholine levels would be at their lowest. The field analytical technique used in (a) was of no value for this study since it does not differentiate between N-trityl morpholine and its hydrolysis product Triphenyl carbinol (Triphenyl methanol). Chromatographic separation of the two compounds was carried out before spectrophotometric analysis of N-trityl morpholine was possible (Beynon & Wright, 1977). From the results the extent of the coverage of the system with lethal concentrations of molluscicide was determined.

(c) Caged sentinel snails

Before each application, cages containing 25 *Biomphalaria pfeifferi* and 25 *Bulinus truncatus* were distributed throughout the minor canals.

The cages were collected after each treatment and the snail kill assessed.

(d) Natural snail population sampling

Thirteen of the 57 minor canals in the pilot area and seven minors in an adjacent untreated area were sampled monthly for snails by taking 20 scoops every 300 m down their length.

(e) Natural infection rates in snails.

(f) Finally incidence studies, by periodic follow-up of a cohort of negatives.

Conclusions

It was from the combined results of all applications that an annual regime was suggested. The regime consisted of four applications per year, two by drip feed supplemented by knapsack spraying, one by drip feed plus aerial spraying and the 4th using airspray alone.

In December 1973, the treated area was expanded to 378,000 acres when five drip feed dispensers were used in series, and the tail ends of some 240 minor canals (120 km) were knapsack sprayed to give a complete coverage of the system. The application was successful but it required careful planning and the spraying element over such a large area proved to be very tedious. To expand this technique to the whole of the Gezira, i.e. to 5 times this size, would be logistically very difficult.

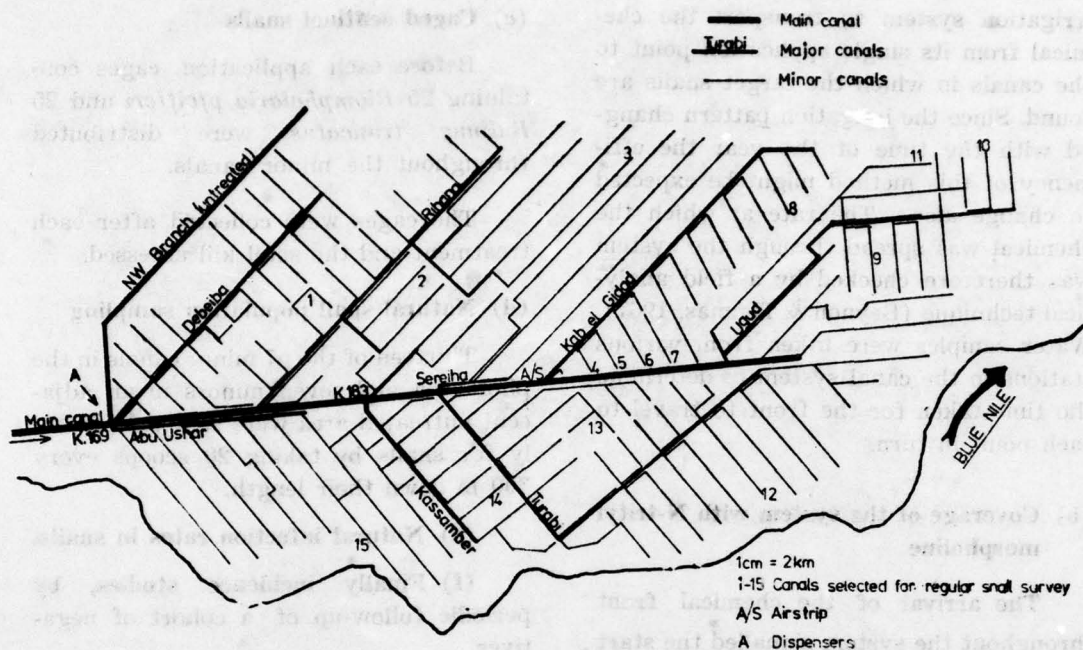


Fig. 1. The Schistosomiasis Research Project area in the northern Gezira, Sudan, showing the 1000 km² treated.

After two aerial sprays which were carried out in March and May 1974 as part of the regime, we reconsidered the proposed drip feed and ground spray for September 1974 and decided to attempt a further airspray even though the area was being irrigated and the canals were full of running water. This new method proved to be successful and a new annual regime of five sprays at 2 ½ months intervals is now being implemented.

In this communication I have only mentioned the objectives of the project, the planning, and the experimental work done on the control aspects.

You will be listening to the other members of the team about the epidemiology and morbidity of the disease, the transmission studies, the actual techniques of molluscicide applications and up-to-date results.

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THE DEVELOPMENT OF AN ANNUAL REGIMEN FOR SNAIL CONTROL IN THE GEZIRA IRRIGATED SCHEME, SUDAN

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This is a further report of the progress of Bilharzia control in the Sudan. Thirteen months ago in Munich, we reported that we had reached an optimum regime for the control of snails on an area of 120,000 acres of the Gezira. This regime consisted of four applications of Frescon per year, namely :

Every September and December

A drip feed to the fast flowing irrigation main canal at approximately 0.1 ppm for 10 days plus knapsack spray of minor canal stagnant tail ends at a concentration of about 0.4 ppm.

In March

A five-day drip feed to the main canal accompanied by the aerial spray at about 0.25 ppm of all minor canals, which are almost stagnant at this time.

In May

A complete airspray at 0.25 ppm to the whole system which is virtually stagnant with up to 40% of the minor canals dry.

We also reported that to expand the area under control it would be necessary to drip feed the chemical from more than one position. An application in December 1973 was described in which five dispensers were used to treat an area of 400,000 acres (see map, Fig. 1) and may I remind

you that this is still only 1/5 of the total area under irrigation. Also the tail ends of the 240 minor canals in the larger area were sprayed.

Although we managed to treat the area successfully, we felt that the necessary knapsack spraying was in fact too laborious to expect it to be carried out in the Sudan on a routine basis. Thinking of the whole of the Gezira, the spray would involve the spraying of the tail end 0.3-0.6 km of some 1300 minor canals, each at least 1.5 km from the next—hard work in an unfavourable climate for a large team of men. Compared to this we knew that aerial spray was hard work for only one person — the pilot. Therefore, we decided it would be worthwhile to attempt spraying all the canals even during the irrigation season because the resultant saving in time spent :

- a) In the field (6 days : 4 days for spraying against 10 days for drip feed),
- b) In overnight supervision of dispensers,
- c) In laborious knapsack spraying,
- d) In transportation,

would make expansion of the area logistically more feasible.

We therefore expanded our area to 200,000 acres. We put in a drip feed for the main canal at 0.06 ppm for 24 hours

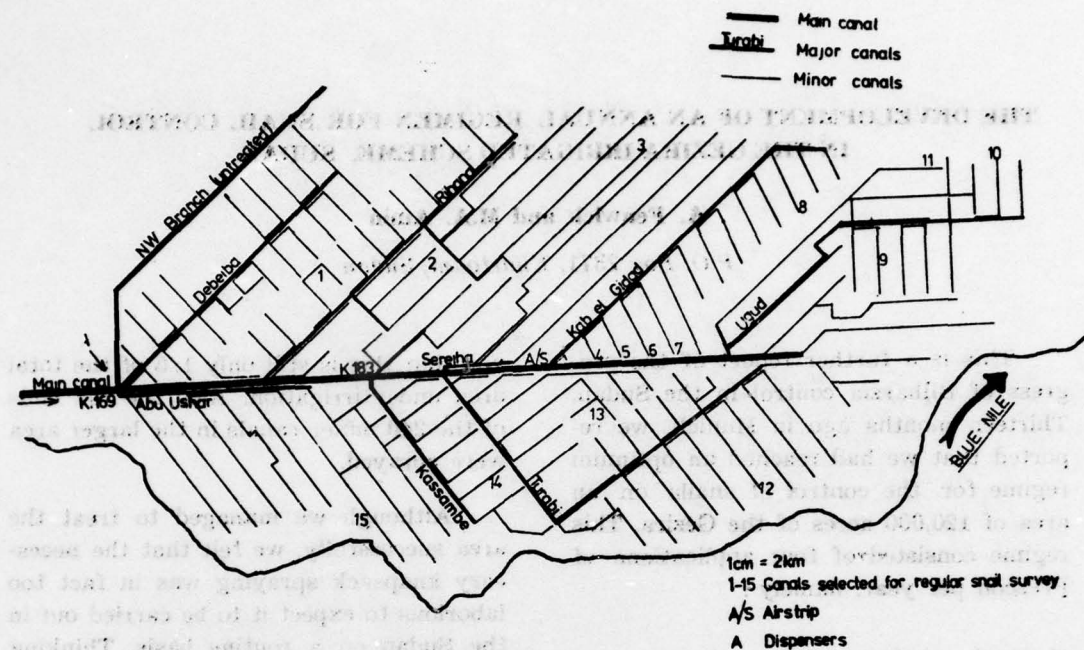


Fig 1. The Schistosomiasis Research Project area in the northern Gezira, Sudan, showing the 1000 km² treated.

and sprayed every canal block by block at a nominal concentration of 0.25 ppm. We have now done this 5 times and have decided on a new regime of five sprays annually at 2½ month intervals.

Over the last 12 months, the snail population in the treated area has varied from zero to 5% of the untreated area, i.e., zero after an application, rising slowly in the last month between applications.

Caged snails distributed around the treated area have always been killed no matter where placed.

A mathematical model of the Gezira designed with the data collected on our large scale drip feed application has now been used to test the application rates that we selected, i.e., 0.25 ppm as the dosage rate (Dr. J. Osgerby, pers. comm.).

It suggests the dose is slightly too high in the minor canals and is too low in the larger main and major canals. We will now continue with this regime making a slight variation in the dosage by increasing the chemical added to the main and major canals.

The cost of the chemical to treat 200,000 acres per annum is 200,000 U.S. dollars. This is about 25% less than would have been used in the drip/knapsack regime. Aircraft hire adds about 5-7% to this cost but labour and transport are negligible compared to chemical cost — and this offsets to some extent aircraft hire.

Epidemiological data are being collected to determine the effect of this control on :

a) incidence of new infections in the 3-9 year age group,

- b) intensity of infections,
 - c) prevalence
- all over a 3 year period.

The result of this work are being given in another room by Dr. Teesdale but, though incomplete, they are beginning to show a promising trend.

One more trial needs to be carried out. That is to repeat a spray with Bay-

luscide in place of Frescon. After this is done in November 1975 we will be able to compare the tests of the two chemicals, taking into account the possibility that fewer annual sprays may be necessary with the ovicidal Bayluscide.

I suggest it would be a brave man who would predict the outcome of this comparison and I hope we will be able to tell you all at a future meeting.

**CONTROL OF SCHISTOSOMIASIS BY THE USE
OF ENDOD IN ADWA, ETHIOPIA :
RESULTS OF A 5-YEAR STUDY**

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Both intestinal and urinary schistosomiasis occur with different prevalences in various parts of Ethiopia. In general, intestinal schistosomiasis is predominant in the highlands, whereas urinary schistosomiasis is largely restricted to the warm and arid lowlands (Russel, 1958 ; Lemma, 1969).

Biomphalaria pfeifferi, the predominant transmitter of *Schistosoma mansoni*, occur in small natural streams in isolated foci in the highlands. *Biomphalaria sudanica* has been reported to transmit *S. mansoni* in some of the Rift Valley lakes. *Bulinus abyssinicus* (and as yet unidentified *Bulinus* spp.) transmit *Schistosoma haematobium* in the Awash and Wabi Shebelle valleys, and the Genale river basin. In the lowlands, where swamps and traditional flood irrigation practices are being rapidly replaced by modern irrigation canals, *Bulinus* snails are flourishing more than ever before. This situation, coupled with the rapid movement of infected and uninfected people in and out of the same area is becoming so serious that it now causes a potential threat to the agricultural development efforts of the country. The problem of schistosomiasis in the major agricultural development areas of Ethiopia may yet lead to what has been encountered in the Gezira project of the Sudan and the irrigated land of Egypt.

Intestinal schistosomiasis due to *S. mansoni* has long been known in the highland areas of the northern province of Tigre, particularly in the town of Adwa. In this and other highland areas where *S. mansoni* is prevalent, it is transmitted in isolated foci in natural streams upon which people depend for their water supply. Adwa was particularly well known for schistosomiasis. About 10 years ago, there was an unusually large number of cases reported from this area, which eventually led to the current epidemiological and control studies (Lemma, 1965 ; Buck et al., 1965).

The molluscicidal properties of the native Ethiopian plant *Phytolacca dodecandra*, known locally as Endod, was discovered in 1964 during epidemiological and ecological studies of schistosomiasis in Adwa (Lemma, 1965). This plant has been used in Ethiopia for centuries as a soap, particularly in the highlands. Its molluscicidal properties were discovered by observing that in areas immediately downstream of where people were washing clothes with Endod more dead snails were found than in areas upstream or elsewhere. Many studies have since been done on the molluscicidal properties of this plant and highly promising results were obtained (Lemma, 1970 ; Lemma et al., 1972 ; Parkhurst et al., in press).

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In 1969, when the potential of Endod for the control of schistosomiasis was apparent, a long-term plan was drawn up to test the plant under natural conditions in the field. The town of Adwa was chosen as it was the place where the molluscicidal properties of Endod were originally discovered and the seriousness of the disease established.

This study involved pre-control baseline data collection on disease prevalence, snail population studies, the proper orientation and education of the people, and involvement of local authorities on an organized campaign against the disease. The program was planned to run for six years. The first year was devoted to pre-treatment baseline data collection and encouragement of cooperation by the people. This was followed by a 5-year continuous effort to control the snail population with the use of locally obtained and quantitatively applied Endod berries.

The effectiveness of the control program was to be measured by the degree of reduction in prevalence rate before and after the control program, with particular emphasis on children between the ages of 1 and 5 years. In an ideal control program where transmission could be completely stopped for a 5-year period, prevalence among children born during that period should be zero. Comparison of prevalence in children of the same age group before and after the 5-year control period should give a measure of degree of success of the program. Results of our effort to control intestinal schistosomiasis chiefly by use of Endod on a community self-help basis in Adwa from 1969 to 1974 are reported here.

Study Area

Adwa

Adwa, a former provincial capital of Tigre province, lies about 1000 km north

of Addis Ababa and 150 km south of Asmara on an all-weathered road.

At an altitude of about 1800 m, Adwa lies in a cradle of mountains, enclosed on 3 sides but open to the west. It is the seat of the Awraja (District) governor, the governorate consisting of 11 weredas or such districts. The area of the study also includes Adi Abun, a suburb of Adwa, where there is a military camp, a 50-bed general hospital, and a regional office for the Malaria Eradication Service.

The 5 churches and one mosque in different parts of the town and the weekly market held on Saturdays, together with the Awraja government activities bring a large amount of human traffic through the town.

The population of the town increased from an estimated 15,800 in 1969 to 17,300 in 1974. About 98% of the people are indigenous Tigreans, 1% are Amharas and the rest are from various parts of the country. About 85% of the people are of the Ethiopian Orthodox Coptic religion, 10% are Muslims and the rest belong to other religions.

Adwa is provided with electricity from a diesel generation plant in Axum, and with a piped water supply from near the source of the Shanna. The main outlet of the piped water supply is in the center of the town, close to the Assem Hotel on the shore of Assem river.

The amount of water available from this source fluctuates considerably, and it never meets the entire water needs of the town. It dries completely during the dry season and the people then depend on the Assem river.

The rivers

There are two main streams in Adwa: Mai (river) Assem, and Mai

Guagua. Mai Assem starts from a small spring to the east of the town in a deeply eroded area of sedimentary deposits. It flows through the center of the town with 2 road bridges over it and finally joins the Mai Guagua 4 km from its source.

Mai Guagua originates many kilometers away from Adwa in the mountains along the road from Adi Abun to Adigrat. In the vicinity of Adi Abun, Mai Guagua is joined by 3 small tributaries: Mai Edaga, Mai Enta, and Mai Shanna (See Fig. 1).

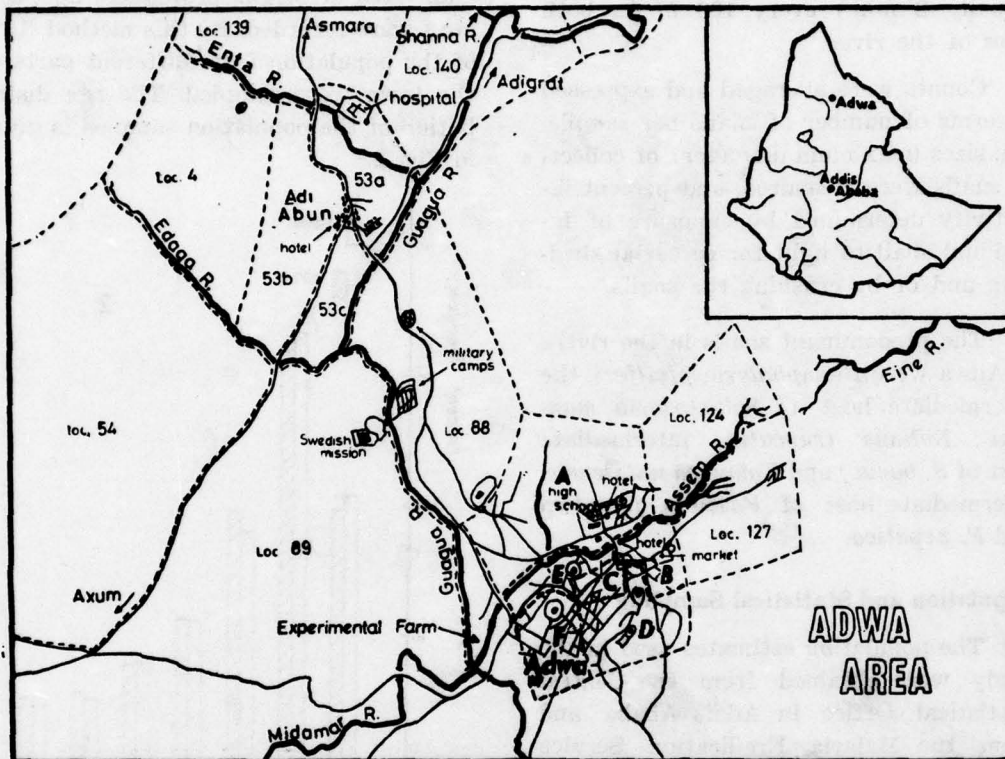


Fig. 1. — Map of Adwa region, Ethiopia

In view of its position, Mai Assem is the most intensively used of the streams in Adwa. Mai Guagua is also frequently used in limited stretches, particularly above and below the Adi Abun bridge. These streams, all of which may become nearly dry in the dry season, provide the fundamental basis of existence for the relatively large populations of Adwa and Adi Abun. They provide water for drinking, cooking, washing, swimming (children), bathing, small-scale irrigation,

local beer (talla) brewing and other domestic uses.

All the streams in Adwa support large populations of *Biomphalaria pfeifferi* throughout the year, and are a hazard for *S. mansoni* infection. The extent of hazard in each case depends upon the frequency of contamination and contact by the people, which differ for different rivers and even different parts of the same river. The pH of the water varies between 7.3 to 7.9 and the temperature between 18° to 26°C, throughout the year.

Snail Survey Techniques

For quantitating the snail population, various methods were tested comparatively. The best was found to be simple visual searching and hand picking by two people for a fixed period of time (usually 2 min.) every 100 m on both sides of the river.

Counts were averaged and expressed in terms of number of snails per sample. The sizes (maximum diameter) of collected snails were measured, and percent infectivity determined by exposure of individual snail to light for cercarial shedding and/or by crushing the snails.

The predominant snails in the rivers in Adwa were *Biomphalaria pfeifferi*, the intermediate host of *Schistosoma mansoni*; *Bulinus truncatus*, intermediate host of *S. bovis*; and *Lymnaea natalensis*, intermediate host of *Fasciola gigantica* and *F. hepatica*.

Population and Statistical Sampling

The population estimates used in the study were obtained from the Central Statistical Office in Addis Ababa and from the Malaria Eradication Service branch office in Adwa.

With aerial photographs obtained from the Mapping and Geography Institute and ground maps made by the Malaria Eradication Service, each family dwelling in the greater Adwa area was numbered serially and the area was divided into zones. Numbers were written on a standard metal sheeting and nailed on each front door. The total number of people living in each zone was determined and the area delineated by specific roads and other landmarks. Ten percent of the population in each zone was then randomly selected for interview and stool examination.

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Random samples of the population were selected by lot. The randomly selected numbers corresponded to specific houses. Each person in the selected house was asked to give a stool sample for examination. Personal data on each individual (area of origin, profession, age, sex, etc.) were recorded. By this method, 10% of the population from different parts of the town were sampled. The age distribution of the population sampled is given in Fig. 2.

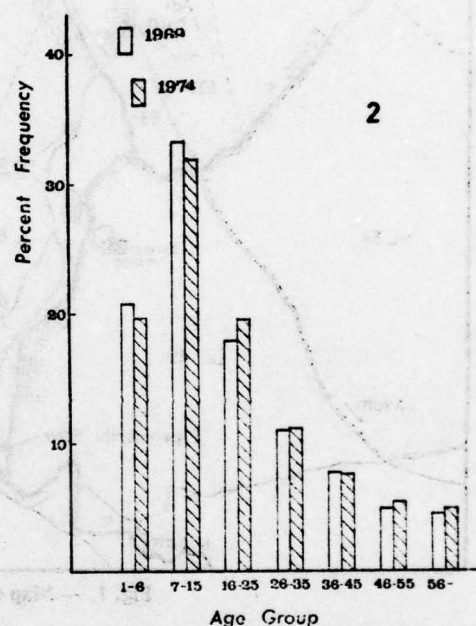


Fig. 2. — Age distribution of population samples in Adwa.

Stool examination techniques

All stool samples taken throughout the control program were examined by one experienced technician (Bahta Mazengia), thus minimizing variation due to individual differences.

Stool examinations were first performed by the direct smear technique, using about 2 mg of fresh stool comminuted with a drop of water on a slide.

Two or 3 such preparations were made from each specimen. All samples negative for *S. mansoni* were further subjected to Ritchie's formol-ether concentration technique (1948), found by Duncan et al. (1970) to be superior to other available methods under our laboratory conditions. Various intestinal parasites other than *S. mansoni*, were also looked for and recorded at the same time.

Endod preparation and application techniques

Endod berries were either bought from the markets in and around Adwa, where it is widely sold as a soap, or berries were collected by hired labour from wild-growing shrubs in the mountains near by. The berries were then dried by direct exposure to the sun for several days, coarsely ground at a local mill and stored as needed. Endod prices in the market varied from Eth. \$ 0.15 to 0.30 (US. \$ 0.07 to 0.15)/kg.

Before use 0.5 kg of crushed berries are mixed with 10 l of water in a watering can. This mixture is poured into the water bodies to be treated. The concentration of Endod at different spots of the treated stream was monitored by two methods: with the use of caged snails and by laboratory determination of the molluscicidal potency of the treated water sample. In the case of caged snails, 10 snails were loosely tied in a piece of cloth attached by a long string and submerged with one end of the thread tied to an easily identifiable object on the shore. After 6 hr of such exposure the snails were washed, fed and allowed to recover in clean water for 24 hr, after which time mortality was recorded. By the other method, samples of water from different parts of the treated river were taken and serially diluted

in clean water. The molluscicidal potencies of the different dilutions were then determined by exposing an appropriate number of snails, usually 10, in each dilution for 24 hr, followed by a proper wash and recovery in clean water for another 24 hr. On the basis of mortality in such dilution, lethal concentrations of Endod in the river water were determined.

Since the primary objective of this project was to determine the usefulness of Endod in the control of schistosomiasis, and as most persons in Adwa become infected in Mai Assem, Endod was systematically used in the treatment of this river.

Other molluscicides used

To compare the effectiveness of Endod with other well-known commercially available molluscicides, Frescon and Bayluscide were also used in some of the streams in Adwa.

Frescon (N-Tritylmorpholine)

The synthetic molluscicide Frescon® (N-tritylmorpholine) was initially tested in Mai Guagua and its three tributaries: Mai Edaga, mai Enta, and mai Shanna. Since the Guagua river originates some 40 km from Adwa, treatment could not be started from the source. Treatment therefore was started about 6 km upstream before it joins Mai Assem at the end of the town. This covered the area where frequent human contact and schistosome transmission was probable. Application was also made above the junction of the three tributaries to Guagua. These tributaries, all only 2-3 km long, were also treated with Frescon. All of these treatments started from their sources until they joined Mai Guagua.

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In all cases Frescon was applied at a concentration of 0.025 ppm (a 16.5% concentration of the active ingredient) for 7 days from a special automatic dispenser, as recommended by Crossland (1967).

Bayluscide® (Niclosamide)

As will be discussed later, Bayluscide was substituted when Frescon was found to be unsatisfactory for treatment of the 3 tributaries and Mai Guagua. Bayluscide was sprayed from a Hudson Spray tank in a mixture of 100 g of the 70% emulsifiable powder in 8 litres of water. The final concentration in the streams was calculated to be about 1 ppm for 8 hr.

Results

Precontrol investigations

Although earlier studies indicated that Adwa was suitable for control of the transmission of schistosomiasis, it was essential that a baseline study be first conducted for later comparison. Prevalence of human infections, and abundance, seasonal fluctuation, and distribution of the intermediate snail host in the area were determined.

To be certain that interruption of transmission could be correctly ascribed to the measures taken, prevalence surveys of *S. mansoni* were also periodically conducted in an untreated control or comparison village, Inticho, about 40 km east of Adwa.

In addition to determination of *S. mansoni* infection rates, data were collected on sex, age, and religion of the sampled population to determine the pattern of infection within the community. Observations were also made on human and animal water-contact activities that might suggest activities likely to increase risk of infection. Such behavioural studies

were conducted before and after the control programme to ascertain whether, during the 5 years of the programme, there were any gross behavioural changes that might have contributed to the reduction of *S. mansoni* infection observed in the controlled area. In spite of efforts to educate the residents about the disease, the water contact behaviour studies conducted before and after the control programme revealed no difference. Details of the behavioural studies will be published separately (Lemma, et al., in prep.).

Stool surveys in Adwa

Results of parasitological surveys by stool examination are given in Tables 1 to 6. Table 1 lists the parasites recorded in the 1969 pre-control survey and the 1974 post-control final survey. Information on the prevalence of *S. mansoni* infection during 1969 and 1974 according to age and sex is given in Table 2.

In 1969, *S. mansoni* was the most abundant parasite in the Adwa area, with 63.1% of the population infected. *Ascaris* (42.2%), *Entamoeba* (16.1%), and *Trichuris* (9.5%) were also found frequently. In general, there were no significant differences in the infection of *S. mansoni* in males and females, suggesting that there were no obvious occupational trends. The figures for males and females in each age group show the usual age distribution of *Schistosoma* infection in a population. There is a rising incidence in the younger members with a peak in the 7-15 year age group, followed by a slight drop in the 16-25 group and a further falling off with increasing age (Fig. 3). The increase in prevalence in the 1-15 age group is associated with increasing exposure, the reduction of infection rate in the older group may be due to reduced exposure or to some sort of acquired immunity.

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TABLE 1. — Stool examinations among randomly selected individuals in Adwa before and after the control programme.

Parasites found	Pre-control 1969 survey		Post-control 1974 survey	
	Number positive	% infection	Number positive	% infected
<i>Schistosoma</i>	1080	63.5	544	33.0
<i>Ascaris</i>	715	42.2	401	24.3
<i>Entamoeba</i>	272	16.1	148	9.0
<i>Trichuris</i>	162	9.5	195	11.8
<i>Giardia</i>	39	2.3	25	1.5
<i>Strongyloides</i>	26	1.5	17	1.0
<i>Hymenolepis</i>	70	4.1	26	1.6
<i>Enterobius</i>	10	0.1	2	0.1
<i>Ancylostoma</i>	24	1.4	14	0.9
<i>Fasciola</i>	3	0.2	1	0.1
<i>Taenia</i>	4	0.2	7	0.4
Negative	223	13.4	597	36.2
Total examined	1659	86.6	1651	63.8

TABLE 2. — *S. mansoni* infection according to age and sex in Adwa before and after the control programme.

1969 Survey							
Age Groups	Number Examined		Number Positive		% infected		Total
	M	F	M	F	M	F	
1-6	229	172	118	84	51.5	48.8	50.2
7-15	380	249	321	206	84.5	82.7	83.6
16-25	150	102	115	69	76.7	67.6	72.2
26-35	60	113	28	51	46.7	45.1	45.9
36-45	52	53	16	20	30.8	37.7	34.3
36-55	50	22	19	13	38.0	59.1	48.6
56	28	35	6	14	21.4	40.0	30.7
Total	949	746	623	457	65.6	61.3	63.5

1974 Survey							
Age Groups	Number Examined		Number Positive		% Infected		Total
	M	F	M	F	M	F	
1-6	145	178	7	17	4.8	9.6	7.2
7-15	224	285	136	140	62.5	49.1	55.8
16-25	122	188	68	59	55.8	31.4	43.6
26-35	59	120	19	31	32.2	25.8	29.0
36-45	42	78	12	13	28.6	16.7	22.7
46-55	37	47	7	6	18.9	12.8	15.9
56	40	39	9	5	22.5	12.8	17.7
Total	669	935	258	271	38.6	29.0	33.8

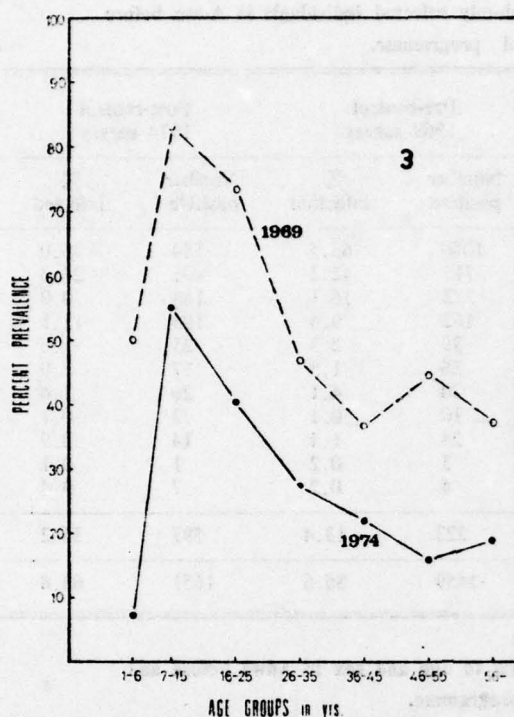


Fig. 3. — Prevalence rates of *Schistosoma mansoni* in Adwa before and after control measures by application of Endod.

Table 3 shows a more detailed analysis of *S. mansoni* infection in the different zones and locations of Adwa. In general, prevalence rates were high throughout and there was no area free of infection. In some areas, i.e. location 124, prevalence was considerably higher than in others, such as location 140 (80% and 43% respectively). This appears to be due to the proximity of a high prevalence location to active transmission sites on the rivers. Location 124 is near an active transmission site on Mai Assem, while location 140 is on the extreme end of Adi Abun near an area known to have very little transmission of the disease on Mai Guagua.

The Adwa Elementary school survey rate in Table 3 corresponds well with the 7-15 age group infection rate shown in Table 2. The low prevalence figure for the Swedish Mission (41%) may be due to the education these students get and also to their being relatively far from active transmission sites.

TABLE 3. — *S. mansoni* infection in different locations in Adwa, 1969 and 1974.

Zone or location	1969 survey		1974 survey	
	No. +/ No. exam.	% infected	No. +/ No. exam.	% infected
Zone A	112/169	67.0	81/217	37.3
Zone B	174/265	65.7	87/248	35.1
Zone C	167/264	63.3	72/206	35.0
Zone D	78/120	65.0	75/159	47.1
Zone E	104/147	70.8	26/98	26.5
Zone F	47/82	57.3	23/73	31.5
Adwa Elementary School	78/93	83.9	—	—
Swedish Mission	20/49	41.0	—	—
Military Camp	61/112	55.0	20/99	20.2
Adi Abun A	63/98	64.3	30/143	21.0
Adi Abun B	54/103	52.4	29/126	23.0
Loc. 4	50/73	68.4	39/95	41.1
Loc. 140	13/30	43.3	—	—
Loc. 54	27/40	60.0	21/43	48.8
Loc. 139	17/33	74.9	—	—
Loc. 127	6/12	50.0	6/16	37.5
Loc. 124	12/15	80.0	—	—
Total	1080/1695	63.7	544/1651	33.0

It was of interest to know whether religion could be a factor influencing rates of infection. Data on the denomination of infected people were recorded both in Adwa and Intitcho. Details are given in Table 4. It seems fairly apparent from this that Muslim men and women show

higher infection rates than do their Coptic peers, and that this can almost certainly be attributed to the ritual washing, «wadu», which Muslims practice, a behaviour which naturally brings them more often into contact with the rivers.

TABLE 4. — *S. mansoni* infection according to religion and sex in Adwa and Intitcho (1969)

Area	Religion	% Infection		
		Male	Female	Total
Adwa (Zones A-F)	Christian (coptic)	62.2	60.5	61.3
	Muslim	69.9	68.3	69.6
Intitcho	Christian (coptic)	23.6	17.6	19.4
	Muslim	30.0	23.5	27.0

Stool surveys in the comparison (untreated) village of Intitcho

Intitcho, a somewhat smaller town than Adwa, located about 40 km east of it, was selected as a reference area to show the progress of the disease where no control measures were being applied. A 10% statistically random sample of the population was followed and stools examined in much the same way as in Adwa.

Table 5 lists all parasites recorded by stool examination in Intitcho during 1969 and 1974. In contrast to Adwa, *Ascaris* (29.2% in 1969, and 22.2% in 1974) remained the most prevalent parasite, with *S. mansoni* (22.6% in 1969, and 16.7% in 1974), and *Entamoeba* (7.5% in 1969, and 16.6% in 1974) following.

Trichuris was only 2.8% in 1969 but rose to 9% in 1974. *Giardia* also rose from 0.9% in 1969 to 6.3% in 1974, while

Strongyloides dropped from 2.8% in 1969 to only 0.7% in 1974. Similar drops in the infection rates of *Hymenolepis*, *Enterobius* and *Ancylostoma* were also observed. As in Adwa, the male population was more heavily infected with schistosomes (Table 6). This is somewhat surprising as the reverse might be expected, since women serve as water carriers and laundresses and presumably have more frequent contact with infected water.

It is interesting to note that because of the Intitcho river being situated in a deep gorge in a relatively difficult position, young children who could not get free access to it were spared from infection with schistosomiasis.

Biodynamics of the snail population

In order to achieve maximum efficiency of control, especially of the snail host, knowledge of seasonal population

TABLE 5. — Stool examinations in randomly selected inhabitants of Inticho during 1969 and 1974

Parasites Found	1969 Survey		1974 Survey	
	No. + out of 106 Examined	% Infection	No. + out of 144 Examined	% Infection
<i>Schistosoma</i>	24	22.6	24	16.7
<i>Ascaris</i>	31	29.2	32	22.2
<i>Entamoeba</i>	8	7.5	21	16.6
<i>Trichuris</i>	3	2.8	13	9.0
<i>Giardia</i>	1	0.9	9	6.3
<i>Strongyloides</i>	3	2.8	1	0.7
<i>Hymenolepis</i>	5	4.7	3	2.1
<i>Oxyuris</i>	4	3.8	1	0.7
<i>Ancylostoma</i>	2	1.9	2	1.4
Negatives	48	45.3	57	39.6

TABLE 6. — *S. mansoni* infection in different age groups and sexes in Inticho

1969 Survey								
Age Years	No. exam.		No. positive		% Infection		Total	
	M	F	M	F	M	F		
1-6	19	8	0	0	0.0	0.0	0.0	
7-15	18	16	6	6	33.3	37.3	35.3	
16-25	6	9	2	1	33.3	11.1	20.0	
26-35	8	7	6	0	75.0	0.0	40.0	
36-45	2	6	1	2	50.0	33.3	37.0	
46-55	2	3	0	0	0.0	0.0	0.0	
56	3	2	0	0	0.0	0.0	0.0	
Total	58	51	15	9	25.8	17.7	22.6	
1974 Survey								
Age Years	No. exam.		No. positive		% Infection		Total	
	M	F	M	F	M	F		
1-6	5	5	0	0	0	0	0.0	
7-15	74	22	16	1	21.6	4.6	17.7	
16-25	17	7	2	3	11.8	42.9	20.8	
26-35	4	5	2	0	50.0	0	22.2	
36	3	2	0	0	0	0	0.0	
Total	103	41	20	4	19.4	9.8	16.7	

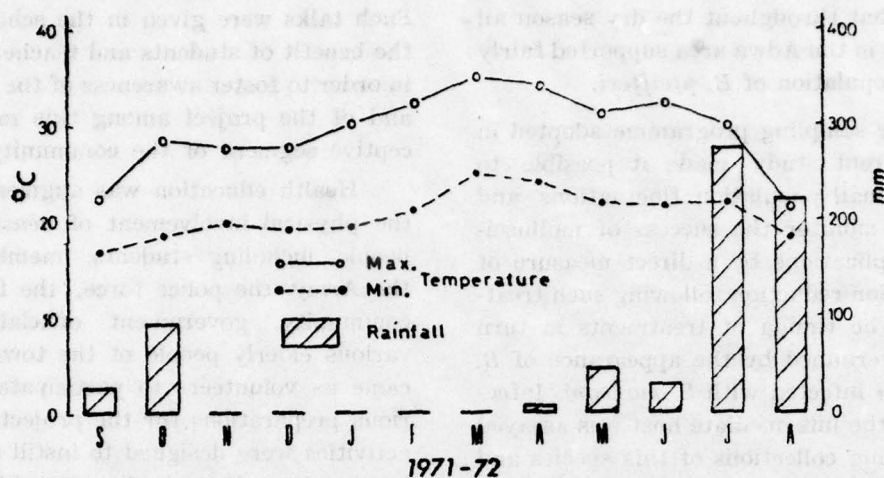


Fig. 4. — Mean temperatures and rainfall, Adwa, Ethiopia.

fluctuation is required. Concomitant infection with *S. mansoni* also requires study, as mollusc populations are subject to rapid and substantial fluctuations, chiefly by temperature and rainfall. In Adwa, it is unlikely that temperature has much effect as it is fairly uniform throughout the year (Fig. 4). Rainfall, however, is restricted to two periods: April-May (short rains) and June-September (long rains). During these times, rain falls chiefly in the form of heavy thunderstorms, small streams become raging torrents for several hours and what might have been a dense snail population of *B. pfeifferi* and other species are virtually eliminated.

Repopulation depends upon the frequency of such rainstorms, but in general small populations survive until the rains ease off. Repopulation is from individuals that survive in sheltered parts of the habitat. Therefore, in order to trace the fluctuations of snail colonies in the various streams, weekly surveys were carried out to determine the abundance and

distribution of snail populations and delineate appropriate intervals for molluscicide application.

Various sampling methods were tested but the only one that could be standardized and was thought to give an adequate population estimate was simple hand-searching. All the streams are extremely rocky, rarely showing much mud or silt and usually consisting of interconnected pools. In the dry season, considerable stretches of the rivers dry up completely. Consequently, fixed sampling sites could not be selected, and a more randomized programme was adopted.

Snail surveys during different times of the year along the entire length of Mai Assem, Mai Edaga, Mai Shanna, Mai Enta, and the first 7 km of Mai Guagua, showed abundant populations of *Biomphalaria pfeifferi*, *Bulinus truncatus* and *Lymnaea natalensis*. *B. pfeifferi* was far more widely and abundantly distributed in all the rivers. This observation conforms to an earlier study (1966-67) by a

student of our Institute, Mr. Fesseha, who found that throughout the dry season all streams in the Adwa area supported fairly dense population of *B. pfeifferi*.

The sampling programme adopted in the current study made it possible to follow snail population fluctuations and also to monitor the success of molluscicide applications by a direct measure of population reduction following such treatment. The timing of treatments in turn was determined by the appearance of *B. pfeifferi* infected with *S. mansoni*. Infection of the intermediate host was assayed by making collections of this species and examining them in the laboratory by either crushing the snails or isolating them individually for cercarial shedding. By either method percentage infection rates could be calculated. Molluscicide applications were begun when the snail population becomes abundant, whether or not any infected snails were found.

Launching of the control programme

Once the preliminary snail surveys and the parasite prevalence in the human population were assessed, control mollusciciding operations were begun; other measures were also taken. These measures, though subordinate to the mollusciciding programme, were undertaken to improve its efficiency, stimulate interest in it, and gain acceptance for the programme by the community of Adwa.

The latter aspect was very ably promoted by the Governor General of Tigre, who showed interest in the work from the start and undertook to address an assembly of the community elders, the priesthood, and local government officials. This followed an inaugural lecture and demonstration given by members of the Institute of Pathobiology on the nature and importance of the disease and

the need for controlling transmission. Such talks were given in the schools for the benefit of students and teachers alike in order to foster awareness of the disease and of the project among this more receptive segment of the community.

Health education was augmented by the physical involvement of nearly 2000 people, including students, members of the Army, the police force, the farming community, government officials, and various elderly people of the town, who came as volunteers to participate in various preparations for the project. These activities were designed to instill a lively interest in and eventual responsibility for the programme, as it was to be maintained on a routine basis for some years after the initial 5-year programme. It was hoped too that a build-up of awareness of the public health importance of schistosomiasis would also provoke interest in other problems in public health, which exist both in urban and rural communities lacking a safe domestic water supply and sewage disposal. It was hoped that improvement in general standards of personal hygiene and modification of habits practiced at the site of water contact would develop and contribute to curtailment of water borne communicable diseases.

It was apparent early that application of Endod in whatever fashion would be greatly facilitated by cleaning up and improving the flow of the river. The first task of the volunteers therefore was removal of impeding boulders, straightening stream flow routes wherever possible, and removal of vegetation. A number of Boy Scouts and boys from the junior high school cut and gathered sufficient wood and thornbush for the construction of fences along certain sections of the stream thought to be most frequented, and likely to be important transmission foci. It was

hoped that such fencing would help in determining or preventing access to the stream and the banks, and thus reduce casual activity such as stream crossing, swimming, and defaecation. The Municipality was also directly involved by the provision of zabanyas (guards) for patrolling the streams to prevent contamination in the most densely populated areas. Unfortunately, both the attempts to fence the crucial areas as well as the guarding system, using small fines, failed. The fences soon were broken up and the wood used for fire. Some of the guards who tried to arrest people found defaecating near the stream, were attacked or chased away, chiefly by gangs of youngsters.

As mentioned earlier, the first application of Endod was made in the presence of a large number of town people. Each subsequent application involved the employment of a number of casual labourers, who also acted as a reminder of the importance of the project and its continuance. Other facets of the programme, such as the annual stool surveys and the frequent visits by Institute staff and visitors, also had this incidental effect of increasing awareness of the control efforts.

A further adjunct to enhanced effectiveness of control measures was a programme for construction of pit-latrines in as many households as possible. A survey made in November 1969 showed that there were 518 latrines in Adwa and Adi Abun, i.e. only one out of 10 houses had such a facility. Of these, perhaps only between 50-100 conformed to the standard 1 m² × 3 m deep hole overlaid by a wooden platform with a suitable opening which is kept covered when not in use to prevent ingress of flies. In a comparable survey in 1974, about 50% of house-holds questioned during the stool

survey claimed to have latrines in their compounds, but only about 19% claimed using the latrine and keeping it in good order. This point will be discussed subsequently.

Molluscicide applications

Endod

As mentioned under Methods and Materials, a mash of Endod berries in water was poured into the river along the shores, with particular attention to the grass growing on the edges, seepage areas, and any ponds at the sides. This method was found to be far more effective than one previously tried that involved dripping concentrated Endod from a locally designed and constructed controlled-flow barrel. The latter was stationed at the head of the river, and the solution was allowed to mix into the river and flow downstream. With this method Endod was not evenly distributed. The centre of the river had high concentrations of molluscicide while the shores did not have enough. Therefore, application of Endod with watering cans were preferred for routine use. With this later method, Endod was applied in sufficient quantities to make up and maintain a final concentration of 80-100 ppm for 6-8 hr which was sufficient to kill snails along the entire Assem river.

By trial and error, it was found that the whole treatment required two teams, each consisting of a supervisor, two sprayers, one man to carry and supply the Endod to the sprayers. One team started at the junction of the Assem with the Guagua and worked upstream, while the other started at the bridge by the Assem Hotel and also moved upstream. In this way, the river was covered in 1½ to 2 hr. Three hours after starting, the teams returned to their starting point and applied the molluscicide once again.

TABLE 7. — Effect of Endod against different snail species using Mai Assem river water (6 hr exposure and 24 hr recovery, average of 3 separate tests in Adwa, April 17-19, 1975)

Snail Species	% mortality at various concentrations of Endod ppm.				
	(100)	(80)	(60)	(40)	(0)
<i>Biomphalaria pfeifferi</i>	100	100	56	22	0
<i>Bulinus truncatus</i>	100	100	100	34	0
<i>Lymnaea natalensis</i>	100	100	100	80	0

From bioassays made on water taken from 6 places equally spaced along the length of the river, it was ascertained that a lethal concentration was maintained throughout during the 6 hr required and indeed for many hours later (Table 7). Even on the following day, large quantities of foam could be seen passing under the Assem bridge. By these procedures, the amount of Endod needed for complete treatment of Mai Assem was 400 to 800 kg, depending upon the water volume, which depended on the time of the year.

With such a treatment of Mai Assem, the following observations were recorded:

1. Small fish, tadpoles and leeches were killed by the concentration aimed at killing snails. But algae, crustaceans and other organisms in the stream did not appear to be affected, and the fish, tadpole and leech populations were quickly replenished. Although no quantitative study was made, no permanent change in the rich flora and fauna of the treated river could be detected over the 5 years of continuous Endod application other than the temporary effects noted. There were no large fish in these streams.
2. Although attempts were made to prevent the use of treated river water by the people and animals for a few days immediately after treatment,

people have often taken home such treated water while it was still foaming and used it for various domestic purposes. No complaints about ill-effects of such water have been received. Both large and small animals have been seen freely drinking freshly treated water from the river, again without apparent ill-effect.

3. Over 95% of the snail population dies within 24 hr of each Endod application. Two to 3 weeks later, very young snails, presumably those hatched from egg-masses not affected by the treatment, were seen. No infected snail appeared in the stream until about 7-8 weeks after treatment, approximately the time required for unaffected snail eggs to hatch, the young snails to be infected, and for miracidia to develop to fully mature cercaria.
4. During the first few days after treatment, the water becomes very clean and clear, which the people appear to enjoy. Furthermore, all miracidia and cercaria are killed and the stream becomes safe for the following 7-8 weeks until newly infected snails begin to shed again. Treatment of the stream also appears to have an adverse effect on other parasites such as *Entamoeba* (which are killed within 5 min. at 100 ppm in the laboratory).

5. Double treatment was employed in an attempt to compensate for the non-ovicidal nature of Endod. The first treatment was followed by a second treatment 2 weeks later to kill young snails that hatched from the unaffected eggs. However, this method proved unsuccessful as some snails survived the second treatment and perpetuated themselves. Further, not all egg masses laid just before treatment hatched within the first two weeks. Some would take 3-4 weeks after the treatment, while others hatch immediately after treatment. This method, which also required more molluscicide, was replaced by routine treatment every 7-8 weeks, in order to control by reduction but not by the elimination of every snail. This method appeared to destroy selectively snails with an infection with *S. mansoni*.
6. One important result of the snail control program was elimination of the *Lymnaea* population in Mai Assem during the first 3 years of Endod treatment, presumably due to the fact that Endod is ovicidal for *Lymnaea* eggs while adult snails are highly susceptible to its lethal action.

Frescon

Frescon was initially tried in Mai Guagua, starting about 6 km upstream before it joins Mai Assem.

The automatic dispenser, constructed with the help of the local representative of Shell Chemical Company, worked well and required a minimum of labour and attention. Lethal concentration of the molluscicide was detected by use of caged snails and chemical analysis. Concentration of the chemical further down stream was, however, so low that it was undetectable by either method. Since the pH of

the river water was about 7.0, hydrolysis of the active principle was not thought to be responsible for this loss in activity. Dilution in some of the large pools at the lower end of the Guagua, and possible loss by absorption of the active ingredient by non-specific materials may be partially responsible.

In an attempt to get an even distribution of Frescon, application from the dispenser was backed up by spraying the stream margins from a Hudson malaria spray tank. In one instance a trial on a 100 m stretch of river showed that on the day following application the number of *B. pfeifferi* fell from 460 to 110, and a few days later only 12 snails could be found in the same portion of river.

In applying Frescon from dispensers into the Edaga, Enta and Shanna tributaries of the Guagua, some of the effects were seen in subsequent snail surveys. However, since these streams flowed so slowly, the chemicals took 4-6 days to cover most of them. Both Edaga and Enta rivers have swampy distal ends and the chemical never reached a lethal concentration there. This was further complicated by the fact that the Guagua and all of the tributaries, particularly the Shanna, dried along portions of the course of the river. This prevented distribution of molluscicide by a single application. Furthermore, because of the non-ovicidal nature of Frescon, as with Endod, frequent applications were required.

For these reasons, the use of Frescon was discontinued in the Adwa streams after the first year and the chemical was replaced by Bayluscide.

Bayluscide

Niclosamide was applied in Mai Guagua and its 3 tributaries from a Hudson spray tank as stated in Materials and Methods. It was sprayed in the

stream to make a final concentration of about 1 ppm for 6-8 hr. Such treatment gave a very good kill and, because of the ovicidal property of the molluscicide, repopulation, particularly in the tributaries that start from springs, was relatively slow. General application was required only about twice a year with some supplementary spot treatments. In Mai Guagua, however, repopulation was more frequent, and general treatment was required every 10-14 weeks. Presumably adult snails were carried down from untreated parts of the river.

As with Endod, Bayluscide also kills small fish and tadpoles, but, again, these organisms quickly repopulate the

streams. Although no quantitative ecological study was done, no ill effect was apparent after continuous application of Bayluscide in the Adwa streams for 4 years.

Evaluation of the control programme (1974)

Evaluation of the mollusciciding programme depended upon stool examinations performed in 1974, after 5 years of control operations. If the measures taken had succeeded in interrupting transmission, reduction in *S. mansoni* prevalence in the community at large would be evident, but the interruption would be especially evident in children aged 1 to 6, as they were born during the

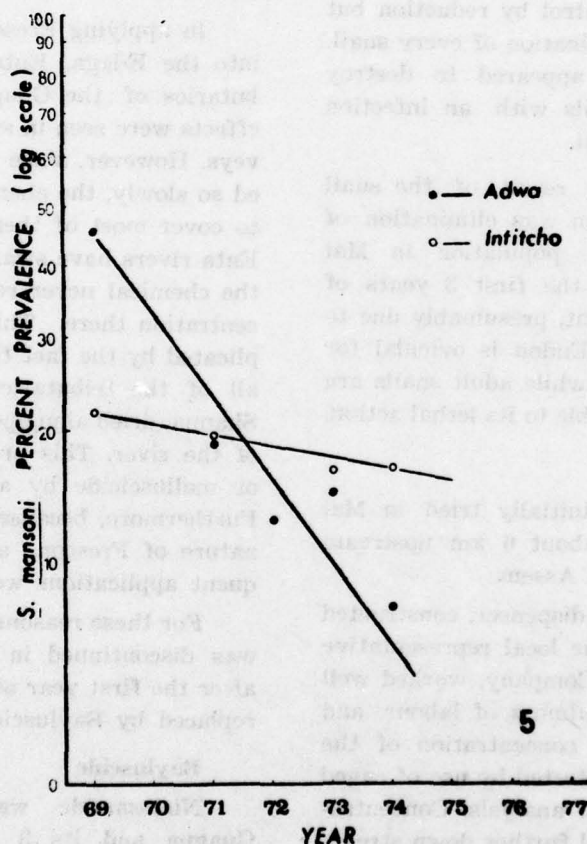


Fig. 5.— Prevalence of *Schistosoma mansoni* in children 1-6 years old in Adwa and in the control area of Inticho.

control programme. Comparison with the control (untreated) village of Intitcho would be another significant indicator (Fig. 3 and 5).

The 1974 stool survey was conducted in much the same way as was the original 1969 survey, utilizing updated maps of the various locations and most recent population statistics provided by the Malaria Eradication Service.

During the parasitological survey conducted in 1974, socio-economic information on the sampled population was also collected for determination of possible correlation between such factors and infection with *S. mansoni*. Observations were also made on water contact activities, as in 1969.

1974 population statistics

The population of Adwa and the surrounding area, including Adi Abun, was estimated by the Malaria Eradication Service at 17,286 in 1973. The comparable figure for the same area in 1969 was 16,369. In 1969 the sample size examined was 1965 individuals or 10.4%. In 1974, the sample taken was 1651 or 9.5% of the population. The age frequency distribution of the 1969 and 1974 samples is plotted in Fig. 1 and shows that the composition of the samples in the 2 surveys were nearly identical.

Results of 1974 stool survey

S. mansoni prevalence in 1969 and 1974 is listed by age group in Tables 2 and 3 and presented graphically in Fig. 2. *S. mansoni* and intestinal parasites data are shown in Table 1. Results of similar surveys for Intitcho, the comparison village, are given in Table 6.

A significant reduction in the prevalence of *S. mansoni* throughout the Adwa community is evident (Table 2); it had dropped from 63.5% in 1969 to 33.8% in 1974, while in Intitcho, it was 22.6%

in 1969 and 16.7% in 1974 (Table 5). Maximum age-frequency prevalence of *S. mansoni* between 1969 and 1974 showed a significant reduction in the 1-6 year age group and some in the 7-15 year age group as well, though peak infection rates in both periods remained in the 7-15 year old group (Fig. 2). Disease prevalence in males in 1969 was similar to that of females (65.6% for males, and 61.3% for females). But after the 5-year control programme more females lost their infections than males (prevalence having been reduced to 38.6% for males and 29% for females). Differences in male and female infection rates may have been due to their respective water-contact activities.

The key feature of the age prevalence distribution change is the dramatic drop in prevalence in the children 1-6 years old. It was equivalent to a reduction of about an 85% in the transmission of the disease. This drop was supported by significant reductions in prevalence among all age groups (Fig. 3).

Table 3 shows the prevalence rate of *S. mansoni* in different locations of Adwa. Some of the locations sampled in 1969 were not included in the 1974 survey as some groups, such as the Adwa elementary school and the Swedish Mission, did not need to be sampled twice, once as part of the population at large and once as a special group. Other areas not sampled in 1974 included locations 140, 139 and 124, all of which had relatively small populations spread over a wide area in a topographically difficult area not accessible by road. It was felt that excluding these small groups would make no difference in the final control assessment.

Interim prevalence surveys by stool examination

Between 1969 and 1974 several addi-

tional surveys were conducted, primarily in the 1-6 year age class to measure prevalence changes in the treated area and the comparison village. Results are shown in Fig. 5. The fall in prevalence in Adwa is fairly steep throughout the 5-year control period, whereas in Intitcho there was no significant change over the 5-year period, the infection remaining about 20%.

Assessment of other factors

In order that reduction in schistosomiasis prevalence can be reasonably ascribed to the snail control efforts, other factors should have remained more or less the same. Several of these factors were dealt with in a questionnaire used in the 1974 survey. Although in many instances answers were ambiguous or conflicting, some useful information was obtained.

Of those questioned 66% claimed to have lived in the same house for more than 5 years, indicating that there was no radical change in the habitat of 2/3 of the Adwa population during the control period. With respect to living standards, 49% claimed it was higher in 1969 than in 1974, and only 10% said that the reverse was true. This was due largely to massive inflation in the price of nearly all foodstuffs on which the bulk of the average Ethiopian income must be spent, with no general compensatory increase in income. No factories, companies, or any other substantial industries opened business in Adwa during the 5-year control period.

As a result of the general drought in the northern part of Ethiopia, particularly during the latter part of the control period, there has been an increased shortage of water in the area. In Adwa, there was more dependence and contact with the rivers which were observed to

be continuously reduced in size and volume.

Although no dramatic change occurred in stability and income level of the people, the town of Adwa did undergo some improvements. The road from Adi Abun to Adwa was paved, the main road and piazza laid out with trees and flowerbeds, a branch of the Commercial Bank of Ethiopia and a new comprehensive High School were opened. These changes, however, had little impact on the patterns of life or activities of Adwa residents. Although strict comparison with the situation prevailing in 1969 is not possible, 38% of the people said in 1974 that they used stream water even for drinking, in spite of the often available piped water supply. Stream bathing was admitted by 44%, and 67% said they washed their clothes in the streams. Other activities, such as children playing in the water, remained more or less the same. Of those laundering at the streams, 59% also bathe, or at least wash their hands and feet. Of those who go to the streams to collect household water, 50% also indulge in other water-contact activities.

According to figures provided by the Municipality of Adwa, 6969 houses and 3,265 latrines existed in Adwa and Adi Abun in 1974, corresponding to 47% of the houses, which is close to the ratio obtained from the questionnaires used during our second stool survey. These figures, possibly exaggerated, show a substantial improvement over 1969. The important factor however, is the use of the latrines. The answers to our questions indicate that latrines were not a favoured place for urination or defaecation. Only 4% of the people admitted to using latrines, 49% preferred the fields and 17% the riverside.

All these relatively high frequencies of water-contact activities, probably all

Cost of Endod		1970-71	1971-72	1972-73
1. Total weight used:		2793 kg	2300 kg	1752 kg
2. Total cost of purchase: Eth. \$		562.20	529.60	438.00
(including transport, storage, coolies, and incidentals)				
3. Average buying price: "		0.20/kg	0.23/kg	0.25/kg
4. Grinding and associated charges, and labour for application: "		304.00	257.05	166.60
5. Total cost of application per year	"	866.20	786.65	604.60
6. Average cost for 3 years per year	Eth. \$	752.5		

Cost of Bayluscide		1970-71	1971-72	1972-73
1. Total weight used:		16.4 kg	19.1 kg	18.7 kg
2. Price paid for in 1970: Eth. \$		16.00/kg	16.00/kg	16.00/kg
3. Total cost of Bayluscide: "		262.40	305.6	299.2
4. Transport and labour for application "		94.50	88.75	121.65
5. Total cost of application "		356.90	394.35	420.85
6. Average cost for 3 years per year: Eth. \$		390.7		

understated, make it probable that no significant behavioural changes have occurred, inspite of the health education efforts attempted at the beginning of the programme.

Chemotherapy, by home treatment or by a doctor was claimed by about 4% of the people. Since the cure rate among treated people is relatively low, and the total number involved was not high, we feel it unlikely that it made a significant impression on the overall transmission rate.

Costs of Endod and Bayluscide used in the Adwa Schistosomiasis control programme

The average yearly direct costs of purchase and application of Endod and Bayluscide used in all the treated streams in Adwa during the first 3 years of the project, 1970-1973, is given above.

Comparison of costs of Endod and Bayluscide

The figures given are the actual costs incurred during the period of 1970-73.

On the basis of cost of treatment of a unit length of river (i.e. km), Bayluscide appears to be considerably cheaper than Endod. However, cost estimation on the basis of per kilometer treatment of river is misleading. It does not take into account the volume of water to be treated and the benefits (in terms of reduction of risk of infection) to the population. For example the Endod treated Assem river has a larger volume of water than any of the Bayluscide treated rivers. Over 80% of the infection with the disease takes place at Assem, thus the benefits gotten from the Endod treatment are much more

significant than those obtained from Bayluscide.

The cost of purchase of Bayluscide has been increasing considerably in recent years. In 1970 a large quantity of Bayluscide was bought at the cost of about Eth. \$ 16/kg and this was what was used throughout the 3-year treatment period. Since then the cost of Bayluscide has been rising at about 10% per annum. More recently the increase has been as high as 30%. Furthermore, Bayluscide had to be bought from Germany with hard-currency. On the other hand the cost of Endod used in these calculations were based on material bought from the local market with local currency during the period of the control programme.

The cost of Endod in the local market has also been rising recently to Eth. \$ 0.30 per kg, because of the high demand and limited supply. The cost of Bayluscide in 1974 was \$ 24/kg (a 50% increase over the cost during 1970). When selected strains of the Endod plant will be grown on a large scale basis, the cost of Endod is expected to fall considerably. In the case of Bayluscide, however, the cost is expected to rise further as a result of inflation and a general rise in cost of commodities in West Germany. If Bayluscide is to be used for snail control on a large scale basis over a prolonged period of time, the government would need to allocate quite an amount of hard currency, a resource which is in great demand for other development projects.

Cost of the control programme per head of the protected individual

Perhaps the best way to determine the cost benefit of such a control programme is to show the annual cost of the control per head of protected individual. The total cost of purchase and applica-

tion of Endod and Bayluscide in the Adwa schistosomiasis control programme was \$ 1,143.2 (\$ 752.5 for Endod and \$ 390.7 for Bayluscide). The approximate population of the area where schistosomiasis transmission appears to have been reduced by 85% due the control effort over a period of 5 years was 20,000. Therefore, the cost of the control programme was about Eth. \$ 0.06 (6 cents) or U.S. \$ 0.03 (3 cents/head/year).

Discussion

The reduction in prevalence of schistosomiasis from 63.5% in 1969 to 33% in 1974 among the general population of Adwa, is highly significant and is strong evidence that this reduction is real and was brought about primarily by the snail control efforts. The people in the community on the basis of answers to the 1974 questionnaire, also feel that there are less people suffering from schistosomiasis in 1974 than in 1969. Furthermore, analysis of hospital records in Adwa show a reduction by about 50% in the total number of schistosomiasis cases appearing at the hospital during this period. Some of the reduction, particularly in the older age group, may have been due to loss of an earlier infection. Yet drop in the infection rate has been gradual, suggesting a cause-and-effect relationship with the control effort.

As would be expected, the greatest reduction in infection was in the 1-6 year age group, with a drop from 50% to 7%, an 85% reduction in transmission; while in the untreated comparison village of Intitcho, the rate has remained more or less the same.

Comparison of prevalence of intestinal parasites with *Schistosoma mansoni* before and after the control period, shows some reduction in prevalence of *Ascaris*

in Adwa, but not in Intitcho. There was also a reduction in prevalence of *Entamoeba*, while infection with *Trichuris* has substantially increased. The remaining parasites were recorded in such small numbers that fluctuations are of doubtful significance. The highly significant reduction in *S. mansoni* is therefore the more striking. The reduction in prevalence of *Ascaris* and *Entamoeba* in Adwa but not Intitcho, while other parasitic infections remained the same, suggest that mollusciciding may also have had a controlling effect on these parasites as well.

The data, in our view, strongly suggest that the primary cause for reduction in transmission of *S. mansoni* in Adwa was the use of Endod to control *B. pfeifferi* in Mai Assem, the centre of activity for the majority of the population of Adwa, and the most highly infected and hazardous river in the area, and not to unrelated events. The control programme has also benefited, though to a lesser extent, from the use of Bayluscide in Mai Guagua and its 3 tributaries.

Continuous surveillance of the streams for snails over the 5-year control period has enabled us to establish the patterns of repopulation following molluscicidal application. This, coupled with snail infection data, allowed us to develop a routine treatment programme for each molluscicide in each stream. On the basis of the last 3 years' application of Endod in Mai Assem, the following schedule is thought adequate for snail and infection control: Endod application every 7-8 weeks through the 9 month dry season, beginning at the end of September after the main rains cease. Using Bayluscide, it was only necessary to treat Mai Guagua every 10-14 weeks, and that primarily because of repopulation of snails from untreated parts of the river. For the other

small streams, application frequency was even less, about 3 applications per year in Mai Enta, and 2 each in Mai Edaga and Shanna. This may be due both to the ovicidal properties of Bayluscide and to the fact that much of the length of these tributaries dry out during the dry season.

The health education aspects of the control effort did not have any great impact in disease control. Water contact behaviour and the water supply system remained much the same. Efforts to fence some particularly hazardous sections were unsuccessful. Defaecation and urination habits on the river shores, particularly near Mai Assem, have remained unchanged. Employment of guards to prevent this did not succeed. The Muslim population was more heavily infected with schistosomiasis than were their Christian neighbors, owing to the obligatory daily ritual washing in infected waters.

The changes observed in the infection pattern at the end of the 5-year control programme closely resemble those seen elsewhere (Barnish, 1975). A shift in the peak of the age/frequency distribution to a slightly older group is a good indication of reduction in transmission. These reductions were brought about by similar mollusciciding programmes. The important observation from the programme was that a simple application of locally acquired unprocessed Endod berries, systematically applied, did control vector snails and interrupt transmission of schistosomiasis.

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ration, the Municipality of Adwa, the Haile Sellassie I University, the World Health Organization, and, during the final year, the U.S. Office of Naval Research.

The Ministry of Public Health, in collaboration with the local administration of Adwa, has now taken over the project and the schistosomiasis control programme is continuing on a permanent basis.

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THE QALYUB RESEARCH PROJECT, EGYPT

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The Ministry of Health of Egypt and the U.S. Centre for Disease Control have recently established a long term collaborative research agreement financed by Public Law 480 funds. The major objective of the study is to evaluate mass chemotherapy as a strategy for the control of bilharziasis, especially that due to *Schistosoma hematobium*, under the conditions prevailing in the Nile Delta.

Although mass chemotherapy as a control strategy has been tested in many parts of the world, including Egypt, with varying degrees of success, these studies have yielded little data on the effect of mass chemotherapy on the level of transmission *per se*. While these studies have measured changes in prevalence and intensity of infection in a given population, they have not determined the degree to which mass chemotherapy has reduced parasite transmission. Consequently, this project is designed to critically determine the effect of mass chemotherapeutic intervention on a community basis on several independent indices of transmission, namely snail infection rates, miracidial densities as determined with sentinel snails, and the incidence of new infections in humans.

To improve the efficiency of irrigation schemes in Egypt, and to reclaim valuable agricultural land, a system of

tunnel drainage has been constructed in recent years in parts of the Nile Delta. Essentially, tunnel drainage consists of converting secondary and tertiary drains into underground conduits made of concrete pipes placed end to end. These empty into the main drain. The effect of tunnel drainage on bilharziasis is unknown. Thus, one of the several objectives of this project is to determine what effect tunnel drainage has upon indices of transmission, prevalence and intensity of human infection, and upon water contact behavior of the population.

The project is being conducted in the Qalyub Area. The 8 study villages, while only 30 min. by car from Cairo, lie in an agricultural region typical of the Nile Delta. They were chosen on the basis of fulfilling the following criteria:

- 1) Population approximately 2,500 to 7,000.
- 2) Typical prevalence of Bilharziasis (*S. haematobium* infection being approximately 50-60%, and *S. mansoni* infection approximately 0-15%).
- 3) Location in areas unlikely to be affected by the rapid urban expansion of Cairo.
- 4) Low mobility of the population. (Most are farmers and work plots of land immediately adjacent to their villages).

5) Ecological comparability of the villages.

Fig. 1 shows the 8 villages and their relationship to the presence or absence of tunnel drainage. Table 1 outlines the basic study design. It is seen that the 8 study villages are assigned to 4 categories (I-IV), each with a different combination of control factors. The villages of Qaranfil and Aghour, in study group I, will receive mass chemotherapy as well as snail control. They are located in an area with tunnel drainage. They were selected because this study group includes treatment with molluscicides, and because they are down-stream from the other study villages. Bahada and Halaba, the villages of study group II, will receive mass chemotherapy alone; they also have tunnel drainage. The other 2 study groups are essentially controls for the first 2 groups. Thus, Sanafir and Kafr Abou Goma' (group III) serve as controls for the villages with tunnel drainage, and group IV villages, i.e., Kharkania and Kafr Shourafa serve as controls without tunnel drainage.

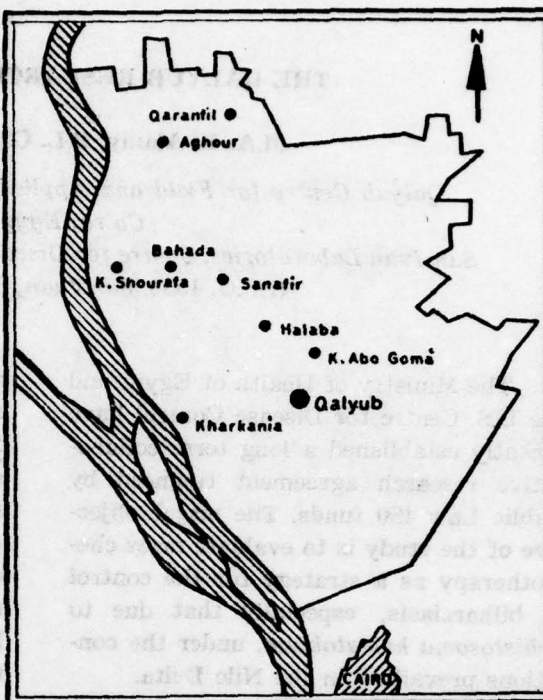


Fig. 1. Study villages of the Qalyub Bilharziasis Research Project. All villages except Kafr Shourafa and Kharkania are provided with a tunnel drainage system.

TABLE 1. Outline of basic study design of the Qalyub bilharziasis research project.

Study group	Control factors			Total	Village
	Mass chemotherapy	Snail control	Tunnel drainage		
I.	×	×	×	3	Qaranfil, Aghour
II.	×	—	×	2	Bahada, Halaba
III.	—	—	×	1	Sanafir, Kafr Abou Goma'
IV.	—	—	—	0	Kafr Shourafa, Kharkania

The study is thus designed so that the effect of individual and combined control strategies can be determined. You will note there is no category for snail control alone. This has been omitted because it is our opinion that snail control *alone* is a relatively expensive indirect long term strategy for interrupting transmission of bilharziasis.

Laboratory support for the project will be provided in a recently renovated, modern facility in Warraq El Arab, a suburb of Cairo. Quality control of laboratory procedures will be assured by collaborating reference laboratories receiving a systematic sample of field specimens (C.D.C. Lab. in Puerto Rico and NAMRU-3 in Cairo).

Note that we have not specified the chemotherapeutic agents or molluscicides to be used. After collecting at least 1 year of baseline data, which we consider absolutely essential to the scientific validity of the study, the decision on what agents to use will be made by a committee appointed by the Minister of Health of Egypt. The committee will base its decision upon benefit/risk relationships of available drugs after thorough evaluation of all available data.

The baseline data alone generated by this project will provide new descriptive information on the distribution, abundance and infectivity of *Bulinus truncatus* and *Biomphalaria alexandrina* snails, and will reflect ecological changes which have occurred during recent years. It will also provide current information on the prevalence, intensity and incidence of human infection in this region, and clinical studies prior to mass chemotherapy will provide objective measures of morbidity caused by *S. haematobium* and *S. mansoni*. Longitudinal observations conducted after mass chemotherapy will reveal the degree to which chemotherapy interrupts progression of the disease. As mentioned previously, the major objective is to determine if mass chemotherapy, alone or in combination with snail control, can result in meaningful interruption of transmission under local conditions. Thorough cost/effectiveness analysis will be done for the alternate control strategies. These data, in combination with information on the effect of tunnel drainage, will greatly enhance the ability to rationally plan programmes for the eventual elimination of Bilharziasis as a major public health problem in Egypt.

THE USE OF TRIPHENMORPH TO CONTROL THE SNAIL HOSTS OF SCHISTOSOMIASIS IN EGYPT

A.P. Warley

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This paper describes the work carried out with the molluscicide triphenmorph in Egypt from 1970-73. Field trials were carried out with the close collaboration of the Department of Snail Control in the Egyptian Ministry of Health.

The objectives of the field trials were :

- a) to determine the required dosage of triphenmorph to control the snail hosts *Bulinus truncatus* and *Biomphalaria alexandrina* in the conditions of the irrigation systems in Egypt ;
- b) to determine suitable methods of application for triphenmorph to an entire irrigation/drainage system ; and
- c) to establish an annual treatment regime.

N-Tritylmorpholine — Triphenmorph

The physical and chemical properties of this molluscicide, its performance against target snails and acceptability studies with crops and non-target fauna have been fully described in publications since the discovery of the compound in 1965 (Beynou, 1971 ; Beynou et al., 1967 ; Chapman, 1967 ; Brown et al., 1967).

More recent studies (Moreton, pers. comm.) on the mode of action of triphenmorph on snails have shown that the chemical acts in a way that is quite different from that of other molluscicides. Chemicals such as niclosamide, pentachlo-

rophenol and the organotin compounds are uncouplers of oxidative phosphorylation. Experiments with *Lymnaea stagnalis* show that triphenmorph acts on the nervous system *via* the synapses, communication between nerve cells being so altered that the normal pattern of spontaneous activity is changed into one of intermittent bursts of very rapid discharge.

Field Trials

Work with triphenmorph prior to 1970 (Crossland, 1967 ; Fenwick, 1970) indicated that the molluscicide was best used by prolonged low dose (PLD) to give full coverage of an irrigation system. The major part of the field work was therefore set up to evaluate this technique in Egypt. A limited number of short-term high dose (STHD) applications were evaluated both within the above study and as a separate trial, when a comparison was made with niclosamide.

Field site

The experimental applications were made within the El-Zummer irrigation system, the end section of the Giza canal.

The El-Zummer (main) canal irrigates approximately 50,000 feddans (21,000 ha) situated a short distance south-west of Cairo. The Zummer canal is divided into three roughly equal lengths by two large sluice gates, so allowing three areas of land (sections) to be successively irrigat-

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ed. Each area is irrigated for 5 days at a time (high rotation) and in the intervening 10 days (low rotation) each area receives substantially less water.

A map of the El-Zummer area is given in Fig. 1. A diagrammatic representation of a typical irrigation/drainage system is given in Fig. 2.

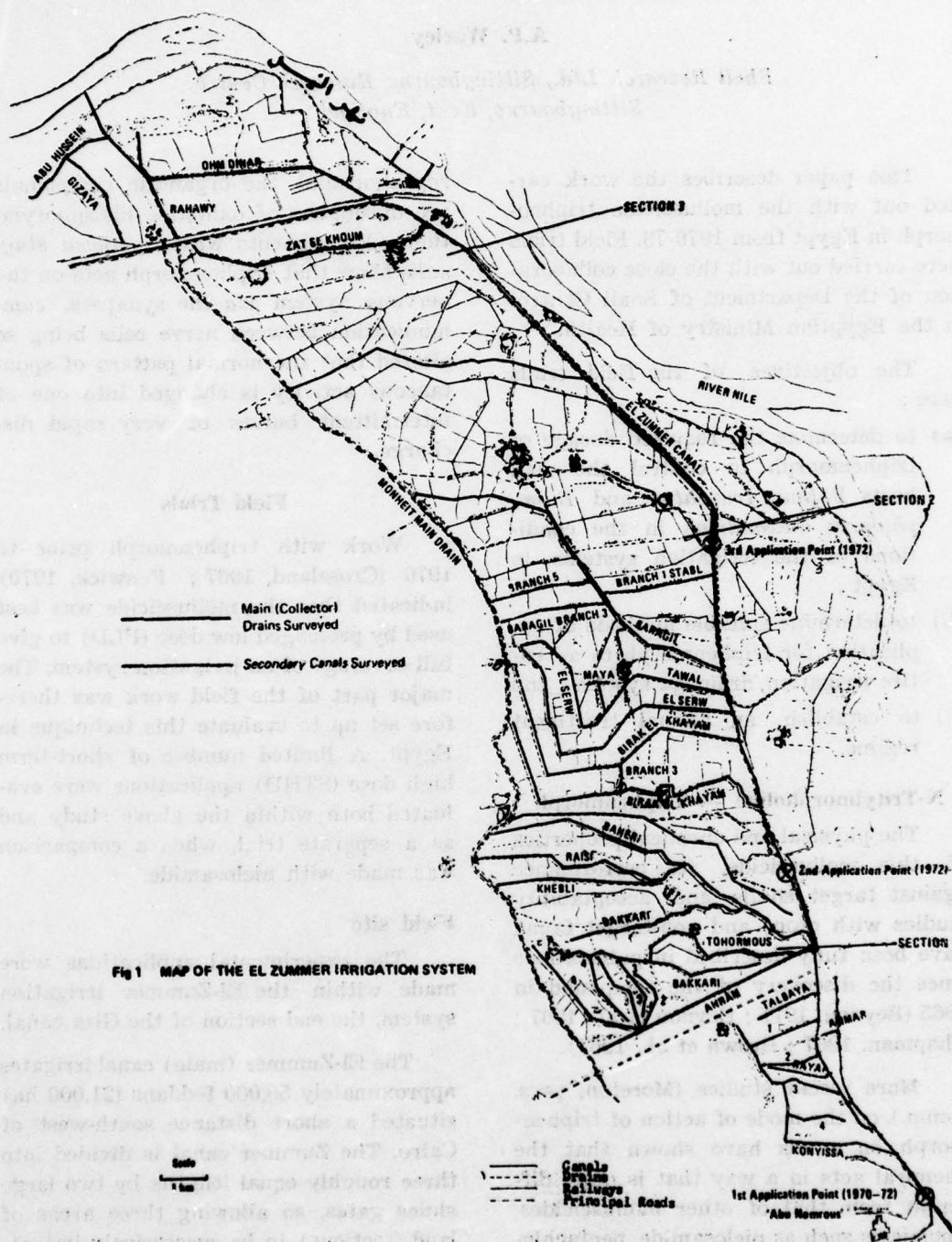


Fig 1 MAP OF THE EL ZUMMER IRRIGATION SYSTEM

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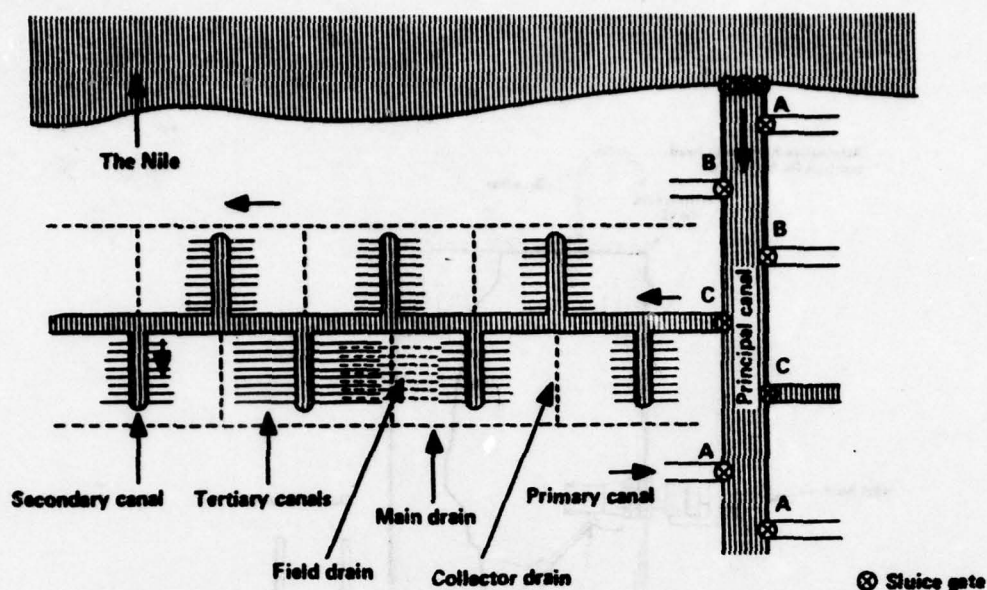
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Section C undergoing irrigation. Sections A and B are closed

Fig.2. Diagrammatic representation of an Egyptian irrigation system
(Not to scale)

Application

FRESCON, the undiluted 16.5% w/v emulsifiable concentrate (EC) of triphenmorph, was applied by gravity feed through a constant head dispenser (Fig. 3). Handspraying was made with Cooper Pegler knapsack sprayers fitted with coarse jet nozzles. The details of all applications are given in Tables 1 and 2.

Prolonged low dose treatments

In 1970 and 1971 FRESCON was dispensed into the El-Zummer canal from one point (Abu Nomrous) at the head of the system for a period of 30 days, initially, (2 full rotations), and for 15 days (1 full rotation) in subsequent applications.

At the end of 1971 the application technique was reviewed. It had been shown that, in theory, considerable savings in chemical could be made by moving the dispenser to the head of the three successive sections for the period of high rotation. It was predicted that a saving of chemical in the region of 25% would be made owing to the following: (1) Successively smaller volumes of water would be treated (i.e. when treating Sections 2 and 3, there is still a considerable volume of water flowing into the secondary canals of Sections 1 and 2 respectively). (2) 'Downstream' losses of the chemical would be minimised, since the distances that triphenmorph was required to travel are cut by two-thirds. Therefore, in the 1972 treatments triphenmorph was applied for 5 days to the head of each section in succession.

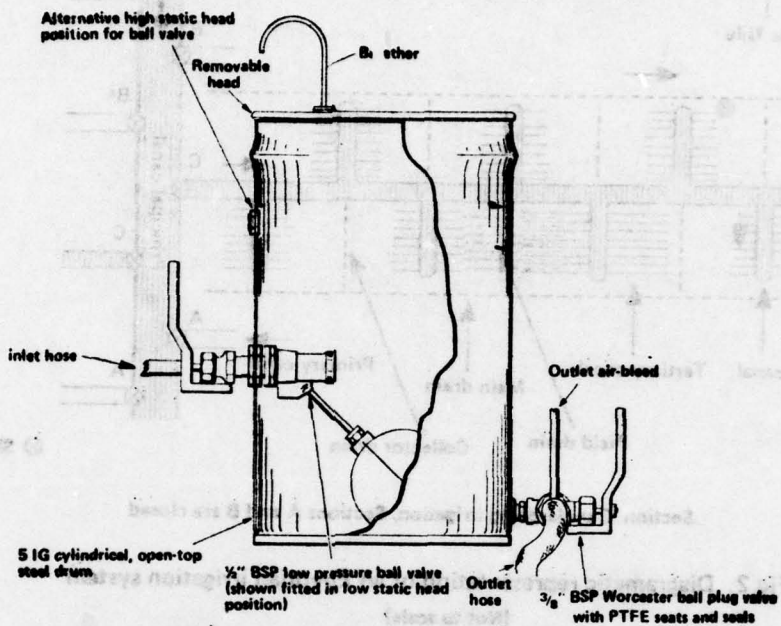


Fig.3a. The FRESCON EC dispenser

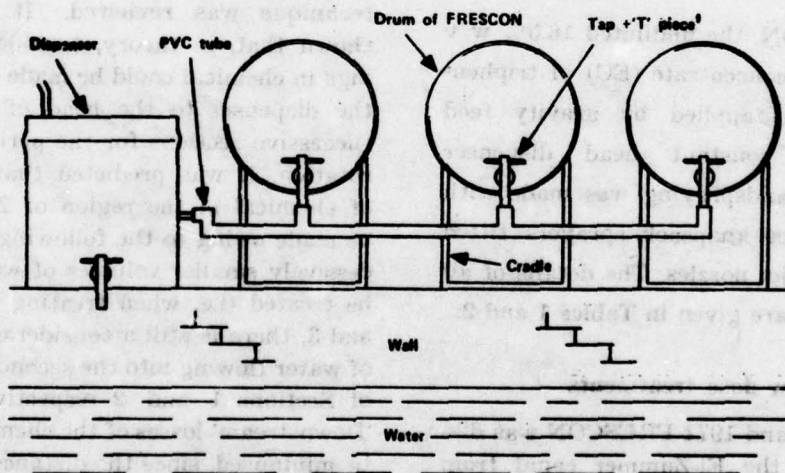


Fig.3b. Mode of application

Short-term high dose treatments

Applications were made to a small number of secondary canals in June and July 1972 (see Table 1).

In April 1973, 3 pairs of secondary canals were selected. One of each pair was treated with triphenmorph EC and the other with niclosamide wettable powder (WP) (see Table 2). An applied concentration of 1 ppm was used for each treatment.

Data Collection

Snail Sampling

Technique. Snail sampling was carried out by a team of 10-20 men, using 2 mm wire mesh, long-handled dip nets. The nets were used to scoop into the weeds at the margin of the watercourse under survey.

A pretreatment survey was made in May 1970. Every watercourse was surveyed, taking one dip sample every metre in the main and secondary canals and main drains. In the field drains and tertiary canals, one dip sample was taken every 20 m. The numbers of infested canals, the length of canals actually infested and the total length of those canals infested, plus snail counts, are given in Table 3. A small proportion of the total watercourses were infested. These infested watercourses were selected as the sampling stations and sampled in all post treatment surveys from May 1970 to October 1972.

In one snail survey (September 1970) 4 (non-sample), secondary canals were surveyed and found to be infested. It appears that snails flourish and decline unpredictably in different canals. The reasons for these fluctuations are not understood.

Bioassay

Freshly collected adult *Bulinus truncatus* (4-10 mm size) were exposed in cages for different periods of time at 4 different stations along the length of 3 of the longer secondary canals in the application of May 1972. After the period of exposure, the snails were transferred to fresh water in the laboratory and assessments of mortality made after allowing a period of 12 hr for possible recovery. The sitting of the caged snails was made to correspond exactly with the location from which water samples were taken for the accurate analysis of free triphenmorph in water. Attempts were also made to assess the silt load in the water at the sampling stations.

Results and Discussion

The data are presented in Tabular and Graphic form at the end of the paper.

1. Assessment of snail control given by prolonged low dose treatment

Natural snail population counts

a) Main Zummar canal (Fig. 4)

The number of snails (*Bulinus*) in the main feeder canals was very considerably reduced by the first three applications and complete control was achieved from August, 1971, to October, 1972, a period of 14 months.

b) Secondary canals (Fig. 5)

In the secondary canals, with the exception of the spring applications of 1971 and 1972, the treatments gave an estimated average 93% kill of *Bulinus* and 100% kill of *Biomphalaria*.

TABLE 1. — Application Details

Type of Application	General drip feed + hand spraying										As 1/6	Spray only
Treatment number	1	2	3	4	5	6	7	8	9	10		
Date	June 1970	October 1970	Ap./May 1971	July 1971	Sept. 1971	Ap./May 1972	June 1972	July 1972	Aug. 1972	September 1972		
Applied drip feed concentration (ppm a.m.)	0.05	0.05 and 0.075	0.05 and 0.075	0.05 and 0.075	0.05 and 0.075	0.035 and 0.04	0.6	0.5 and 1.0	0.075	2.0		
Period of application (days)	30	15	15	15	15	15	2 hours	4 hours	15	5 secondary canals sprayed in low rotation		
Number of application points	1	1	1	1	1	3	1 for each of 5 secondary canals	1 for each of 4 secondary canals	3	—		
Applied spray dosage (ppm a.m.)												
1) Tail ends (last 500m) of all secondary canals sprayed	Not sprayed	0.25	0.25	0.25	0.25	0.25	0.5	0.5	0.5	—		
2) Tertiary canals	Not sprayed	0.25	2	2	2	0.25	2	2	2	—		
3) Main drains	0.5/1.0	2	2	2	2	0.5	1.0	2	2	—		
4) Field drains	0.5/1.0	2	2	2	2	0.5	1.0	2	2	—		
Quantity PRESCON Drip fed (litres)	13,844	7,287	6,640	8,954	7,386	3,584	207	192	6,048	—		
Quantity FRESCON Sprayed (litres)	136	808	1,013	718	627	222	122	38	95	195		
Total FRESCON applied (litres)	13,980	8,095	7,653	9,672	8,013	3,806	329	230	6,143	195		

TABLE 2. — Application details of the short term high dose treatment comparison

Treatment	Canal	Length (km)	Area irrigated (feddans)	Discharge (m ³ /min)	Actual amount used		Total	Quantity formulation per feddan
					Drip fed	Sprayed		
triphenmorp								
Birak El Khayam		9.25	2,418	155	336 litres	20 litres	356 litres	148 ml
Zat El Khoun		6.30	4,821	105	336 litres	20 litres	356 litres	118 ml
Raisi								
Baheri		10.00	4,680 1,114	295	861 litres	36 litres	897 litres	154 ml
niclesamide								
El Serw		7.50	2,062	132	88 kg	2 kg	90 kg	43.6 g
Ohm Dinar		6.80	4,528	204	142 kg	1 kg	143 kg	31.6 g
Ahram		6.00	2,511	111	66 kg	2 kg	68 kg	27.0 g

Both molluscicides were applied at a concentration of 1 ppm a.n. for 8 hr.

TABLE 3. — Summary of the pre-treatment snail survey in the El-Zummer system - May 1970

Type of watercourse	Number		Length in kilometres		Numbers of snails		
	Surveyed	Infested	% of Total	Surveyed	Infested	% of Total	<i>Bulinus</i> <i>Biomphalaria</i>
Main Feeder El Zummer Canal	1	1	100	26	26	100	211 0
Secondary canals	48	14	29	141	62	44	930 0
Tertiary canals	3,143	41	1.3	361	23	6.5	74 6
Main drains	46	21	46	155	60	39	370 1,637
Field drains	958	13	1.4	246	62	2.5	28 149

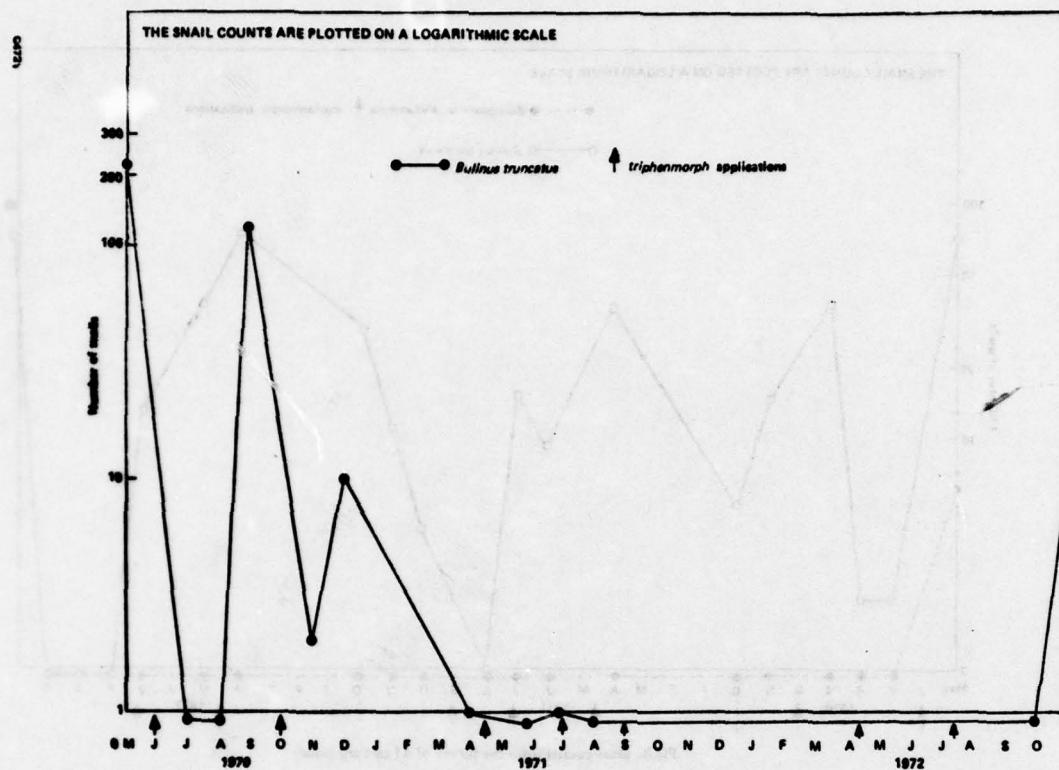


Fig. A. Snail counts from surveys in the main El Zummar canal

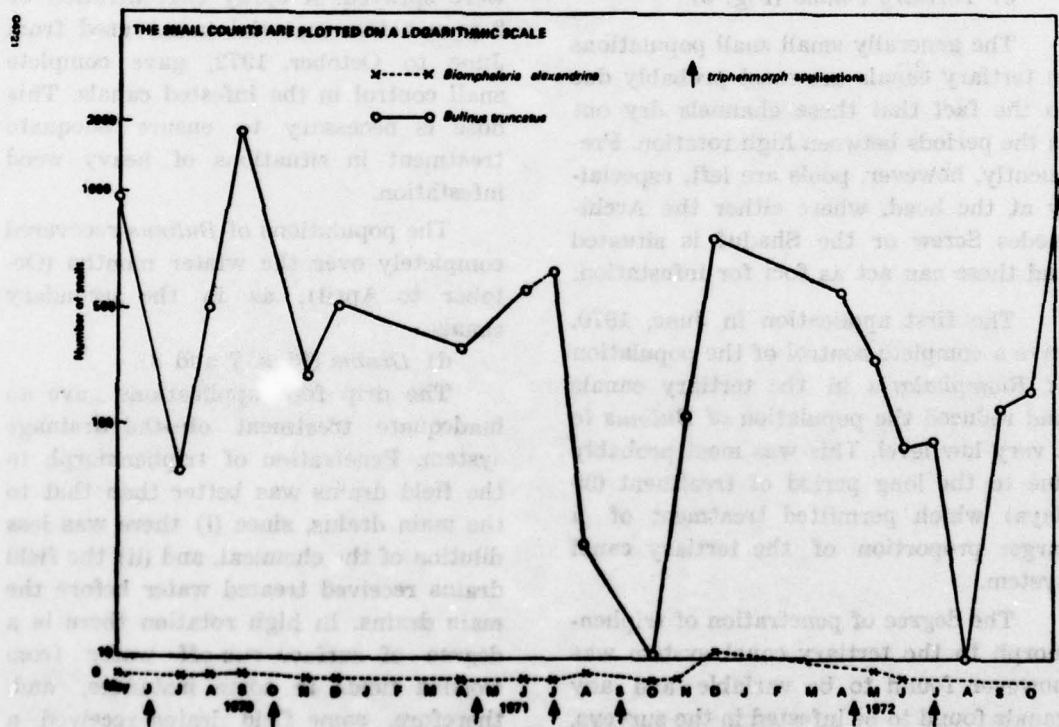


Fig. B. Snail counts from surveys in 16 secondary canals

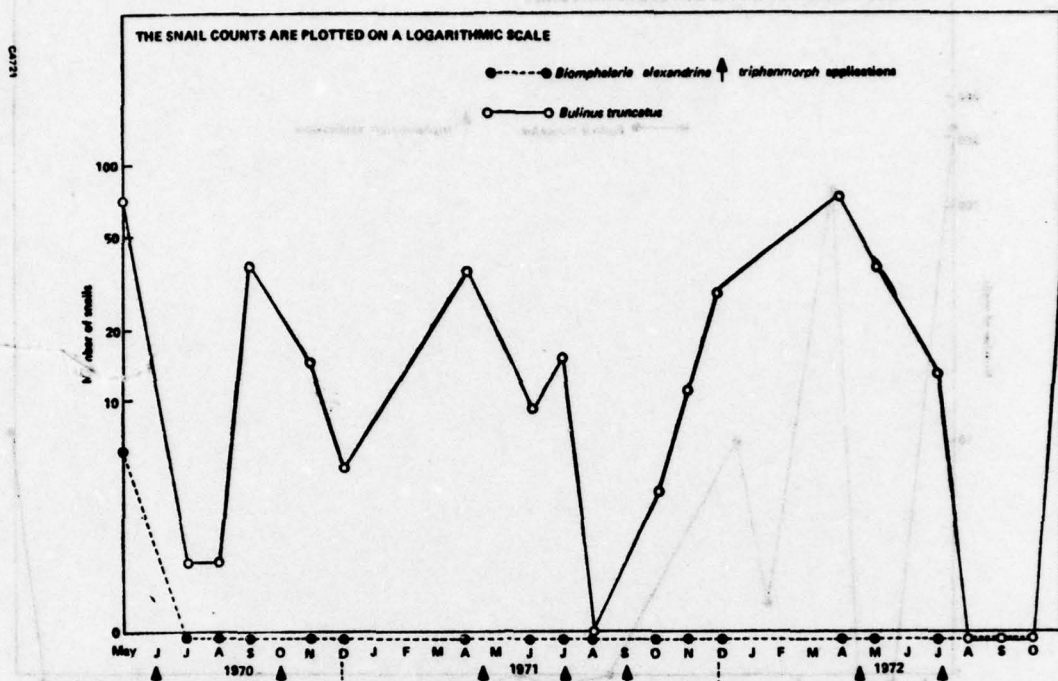


Fig. 6 Snail counts from the survey of 41 tertiary canals

c) Tertiary canals (Fig. 6)

The generally small snail populations in tertiary canals are most probably due to the fact that these channels dry out in the periods between high rotation. Frequently, however, pools are left, especially at the head, where either the Archimedes Screw or the Shaduf is situated and these can act as foci for infestation.

The first application in June, 1970, gave a complete control of the population of *Biomphalaria* in the tertiary canals and reduced the population of *Bulinus* to a very low level. This was most probably due to the long period of treatment (30 days) which permitted treatment of a larger proportion of the tertiary canal system.

The degree of penetration of triphenmorph to the tertiary canal system was however found to be variable and any canals found to be infested in the surveys,

were sprayed. A spray concentration of 2 ppm active material (a.m.) used from June to October, 1972, gave complete snail control in the infested canals. This dose is necessary to ensure adequate treatment in situations of heavy weed infestation.

The populations of *Bulinus* recovered completely over the winter months (October to April), as in the secondary canals.

d) Drains (Figs. 7 and 8)

The drip feed applications gave an inadequate treatment of the drainage system. Penetration of triphenmorph to the field drains was better than that to the main drains, since (i) there was less dilution of the chemical, and (ii) the field drains received treated water before the main drains. In high rotation there is a degree of surface run-off water from flooded fields in some instances, and, therefore, some field drains received a

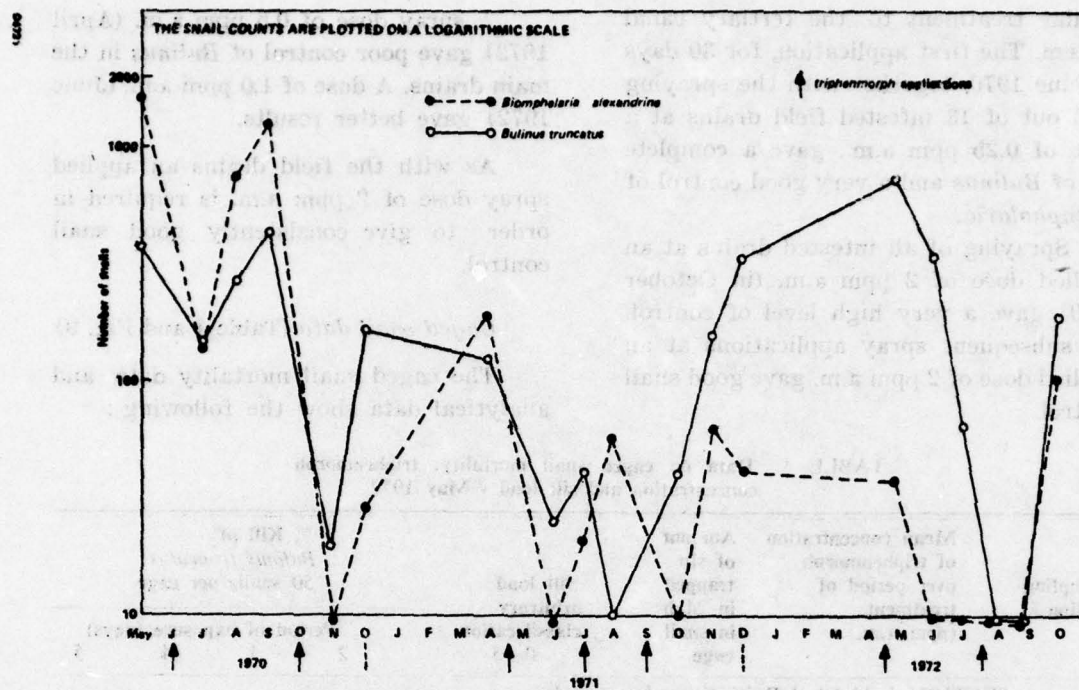


Fig. 7. Snail counts from the survey of 21 main drains

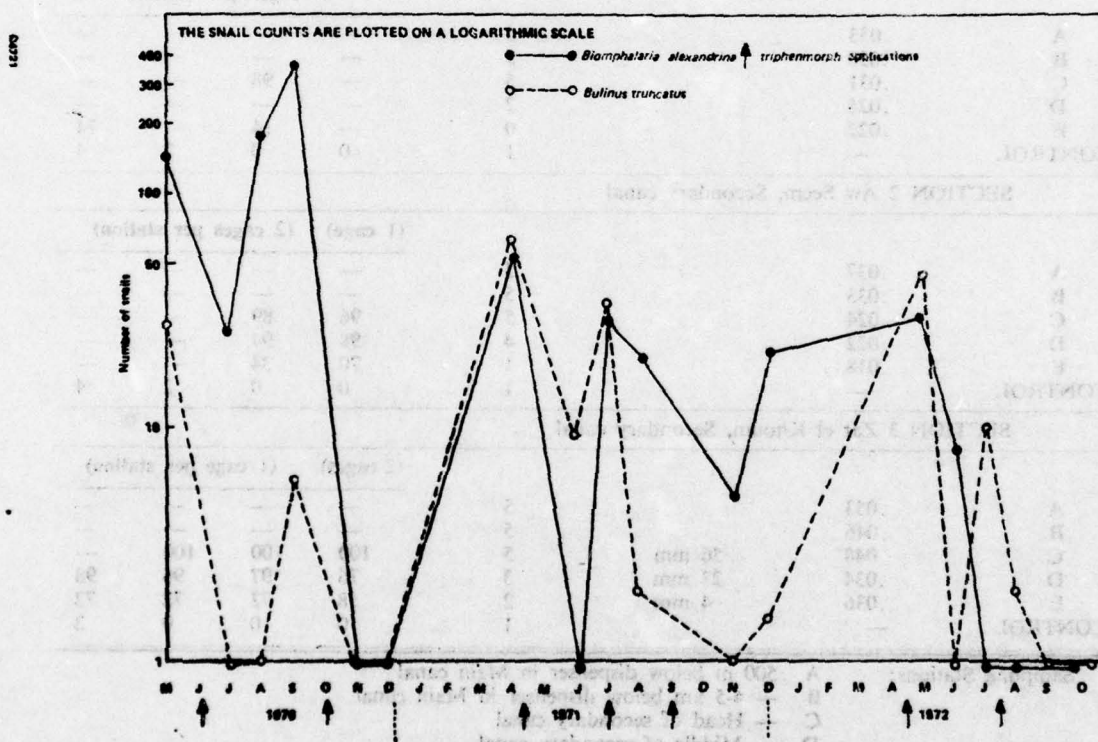


Fig. 8. Snail counts from the survey of 13 field drains

similar treatment to the tertiary canal system. The first application, for 30 days in June 1970, together with the spraying of 3 out of 13 infested field drains at a dose of 0.25 ppm a.m., gave a complete kill of *Bulinus* and a very good control of *Biomphalaria*.

Spraying of all infested drains at an applied dose of 2 ppm a.m. (in October 1970) gave a very high level of control. All subsequent spray applications at an applied dose of 2 ppm a.m. gave good snail control.

A spray dose of 0.5 ppm a.m. (April 1972) gave poor control of *Bulinus* in the main drains. A dose of 1.0 ppm a.m. (June 1972) gave better results.

As with the field drains an applied spray dose of 2 ppm a.m. is required in order to give consistently good snail control.

Caged snail data (Table 4 and Fig. 9)

The caged snail mortality data and analytical data show the following :

TABLE 4. Data on caged snail mortality, triphenmorph concentration and silt load - May 1972

Sampling station	Mean concentration of triphenmorph over period of treatment (ppm a.m.)	Amount of silt trapped in 24 h in snail cage	Silt load arbitrary classification 0-5	% Kill of <i>Bulinus truncatus</i> 50 snails per cage			
				Period of exposure (days)			
				2	3	4	5
SECTION 1 Abdel el Raisi, Secondary canal							
				(4 cages per station)			
A	.033		5	—	—	—	—
B	.030		5	—	—	—	—
C	.031		5	—	98	—	—
D	.025		2	—	—	—	—
E	.022		0	—	14	—	74
CONTROL	—		1	0	0	2	4
SECTION 2 Aw Seem, Secondary canal							
				(1 cage)	(2 cages per station)		
A	.037		5	—	—	—	—
B	.033		5	—	—	—	—
C	.024		5	96	89	—	—
D	.022		4	98	94	—	—
E	.018		1	70	34	—	—
CONTROL	—		1	0	0	2	4
SECTION 3 Zat el Khoum, Secondary canal							
				(2 cages)	(1 cage per station)		
A	.053		5	—	—	—	—
B	.046		5	—	—	—	—
C	.048	56 mm	5	100	100	100	—
D	.034	23 mm	3	76	97	96	98
E	.036	4 mm	2	18	72	72	72
CONTROL	—		1	0	0	0	2

Sampling Stations: A 500 m below dispenser in Main canal
 B — 4-5 km below dispenser in Main canal
 C — Head of secondary canal
 D — Middle of secondary canal
 E — End of secondary canal

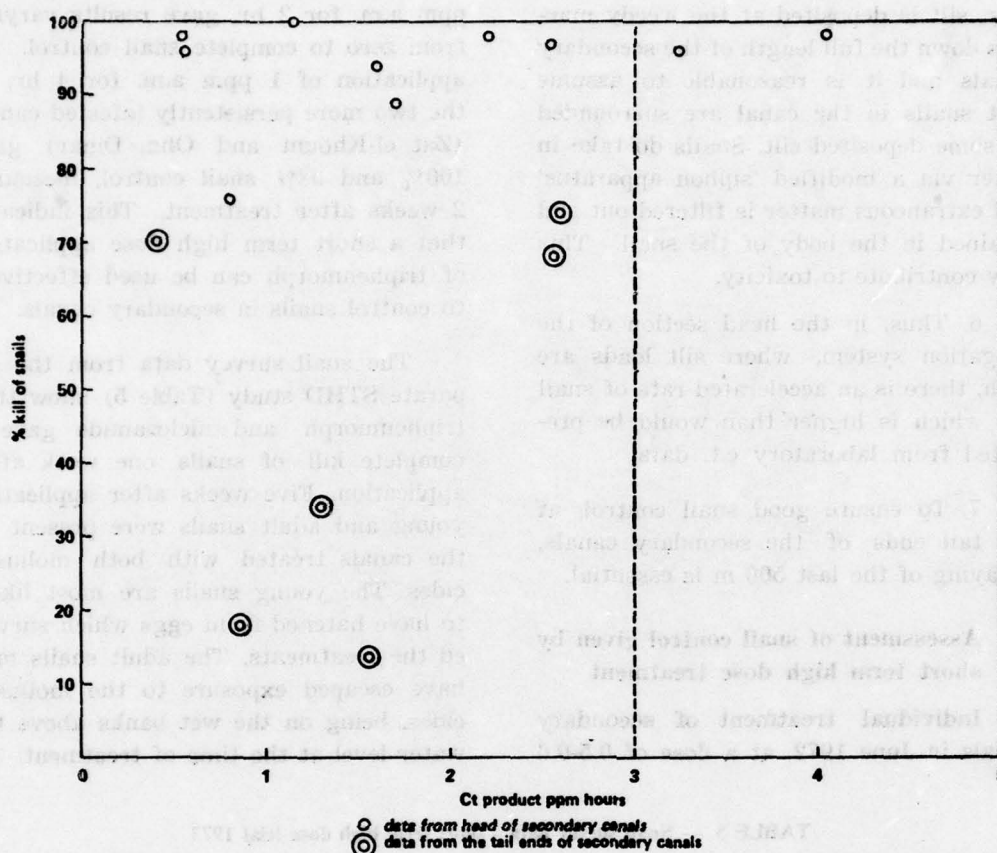


Fig-9. Variation of percentage kill of *Bulinus truncatus* with concentration x time product from caged snail data

1. There was typically a decrease in the concentration of triphenmorph from the head to the tail section of a secondary canal.

2. There was also a decrease in the silt load towards the ends of secondary canals due to a progressive decrease in water flow rate and, hence, an increase in the rate of silt sedimentation.

3. Laboratory and field tests show that silt adsorbs triphenmorph and, hence, this sedimentation results in a depletion of the chemical from the water phase towards the tail end of the secondary canals.

4. There was a rapid mortality of snails caged at the head and mid sections

of a secondary canal where the measured concentrations of free, unadsorbed triphenmorph were, in some cases, only marginally higher than those in the tail end section, but the silt loading was significantly higher.

5. The biological implication is that the triphenmorph which is adsorbed onto the silt is active and that, in fact, the snails are exposed to 2 sources of the molluscicide, one free in-water and the other associated with silt. The snail cages were seen to 'filter out' a considerable amount of silt from the water which could mean that an artificially higher mortality may occur in cages than would be normal in the head sections of the canal. How-

ever, silt is deposited at the weedy margins down the full length of the secondary canals and it is reasonable to assume that snails in the canal are surrounded by some deposited silt. Snails do take in water via a modified 'siphon apparatus' and extraneous matter is filtered out and retained in the body of the snail. This may contribute to toxicity.

6. Thus, in the head section of the irrigation system, where silt loads are high, there is an accelerated rate of snail kill which is higher than would be predicted from laboratory c.t. data.

7. To ensure good snail control at the tail ends of the secondary canals, spraying of the last 500 m is essential.

2. Assessment of snail control given by short term high dose treatment

Individual treatment of secondary canals in June 1972, at a dose of 0.5-0.6

ppm a.m. for 2 hr, gave results varying from zero to complete snail control. An application of 1 ppm a.m. for 4 hr, to the two more persistently infested canals (Zat el-Khoum and Ohm Dinar) gave 100% and 98% snail control, measured 2 weeks after treatment. This indicates that a short term high dose application of triphenmorph can be used effectively to control snails in secondary canals.

The snail survey data from the separate STHD study (Table 5) show that triphenmorph and niclosamide gave a complete kill of snails one week after application. Five weeks after application young and adult snails were present in the canals treated with both molluscicides. The young snails are most likely to have hatched from eggs which survived the treatments. The adult snails may have escaped exposure to the molluscicides, being on the wet banks above the water level at the time of treatment.

TABLE 5. — Snail survey data - short term high dose trial 1973

Treatment <
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Conclusions from the Field Trials

1. Dose and concentration x time product (c.t.)

The data from the El-Zummer trials show that a c.t. product of 3 ppm/hr will control *Bulinus truncatus*. This is fully confirmed by similar studies in the Sudan Gezira scheme (Dazo et al., 1966). A c.t. product of only 1 ppm/hr is necessary for *Biomphalaria alexandrina*.

Once the c.t. product has been established, various permutations of the two parameters, time and concentration can be used, within practical limits. This offers a versatility of use, allowing the application to be fitted into any irrigation system in Egypt.

Thus an exposure of

8 hours at 0.375 ppm
or 3 days at 0.042 ppm
or 5 days at 0.025 ppm
or 7 days at 0.018 ppm

will all give control of *Bulinus truncatus*.

The concentrations that need to be applied to give a c.t. product of 3 ppm/hr for a range of exposure periods and times of flow from the point of application to the end of the system under treatment are given in Fig. 10.

2. Downstream travel of triphenmorph

In static or slow flowing water the rate of decomposition of the compound is governed only by the pH of the water. It is a first order kinetic reaction and follows the equation (Beynon et al., 1967):

$\log_{10} t_{1/2} = \text{pH} - 6$ where $t_{1/2}$ = half life.
The pH of the water in Egyptian irrigation systems (and that of the Sudan Gezira) is in the range of 7.8-8.0. The expected half life should therefore lie

between 70-100 hr. Samples of water (pH 7.8) taken from the El-Zummer canal and treated with triphenmorph in the laboratory showed the compound to have a half life of approximately 70 hr, as predicted. Water sample studies made in the main canal and the secondary canals showed however that triphenmorph had a half life of only 30 hr at the same pH. This was confirmed by similar studies made in the Sudan Gezira (Amin & Fenwick, 1975; Amin et al., in prep.).

The difference is due to the fact that triphenmorph is adsorbed onto silt particles and when silt sediments out of the slower moving water towards the end of the irrigation system there is a natural loss of molluscicide from the water stream. Whilst there is good evidence to show that treated silt is still molluscicidal and probably contributes significantly to the control of snails this factor does impose clear limits on the downstream travel of the compound. For the purpose of siting dispensers and calculation of the required applied dose levels, triphenmorph is taken to have a nominal half life of 30-hours in Egyptian irrigation water.

For main canals that have a flow rate of 2-3 km/hr this means that a given applied dose of triphenmorph will be reduced by half, after travelling for 60-90 km.

For primary canals with flow rates of 1.5-2 km/hr the distance is 45-60 km and for secondary canals with flow rates of 0.5-1.5 km/hr a distance of 15-45 km is relevant.

3. Treatment schedule

A single treatment with triphenmorph to an irrigation system gives very good snail control for approximately 8 weeks. It has been established by Dazo et al. (1966) and Hairston (1965) that

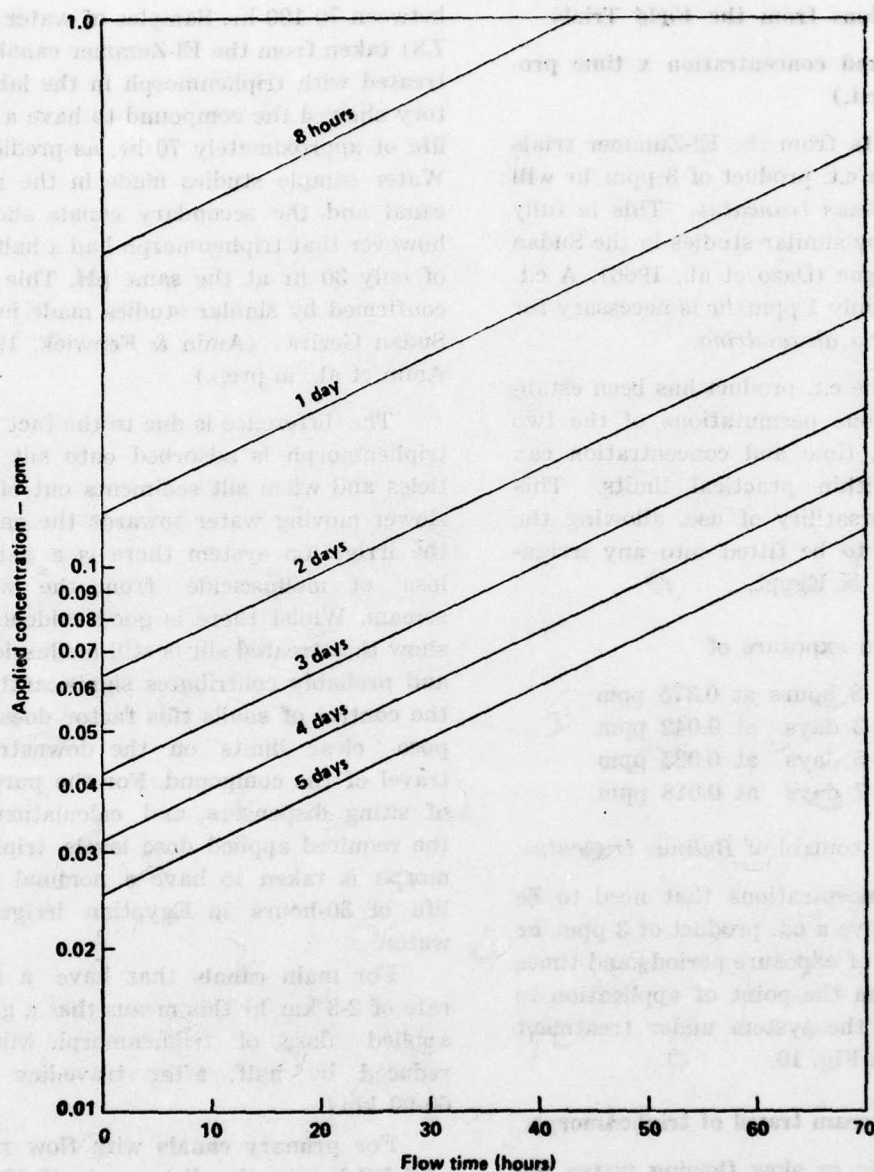


Fig.10- Relationships between applied concentration and flow time for a Ct product of 3 ppm hours for different values of exposure time

snail populations and snail infestation rates are at a minimum in the months November-April in Lower Egypt. This, together with the closure of the canals and decreased human contact with water in this period means that there is negli-

gible disease transmission in these months. It is now accepted therefore that snail control measures made from March to October are sufficient to control disease transmission (Mousa & Ayad, 1972).

Eradication of the snail hosts is virtually impossible, and indeed not necessary to break transmission. Snail breeding reaches a peak in June with an infection rate of about 0.32%. A 95% kill of snails will therefore reduce the infected population to about 0.04% : equivalent to that in the winter months. This is likely to be a conservative estimate of control since infected snails are known to be more susceptible to molluscicides than healthy, non-infected snails. The following annual treatment regime is suggested, based on the present knowledge of the population dynamics of both the snail hosts and the schistosome and the performance of triphenmorph.

I. Early March — First comprehensive treatment of all irrigation channels and drains in the area before snail breeding starts. Water rotations are not in operation in this month which greatly facilitates application.

II. May — Second comprehensive treatment to contain the spring snail population and prevent peak disease transmission in June.

III. June-August — Spot treatments of infested canals and drains.

IV. September . . Third comprehensive treatment to control the second peak of snail numbers and disease transmission.

4. Application

The application of the EC formulation of triphenmorph from gravity feed dispensers is simple and easy to operate, requiring a minimum of supervision. The equipment is inexpensive and can be made locally. Likewise application by knapsack or motorised sprayer is simple to carry out.

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**SCHISTOSOMIASIS INTERVENTION THROUGH THE USE OF
CONTROLLED RELEASE MOLLUSCICIDES :
A REVIEW OF LABORATORY AND FIELD EVALUATIONS**

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The conventional approach to interruption of the schistosomiasis transmission cycle has been mainly through destruction of the host snail by the use of molluscicides. The particular toxicant used and the dispersal method depends upon both economy and a number of environmental factors. Four molluscicides are in widespread usage, although one, sodium pentachlorophenate is being gradually eliminated. A brief review of their advantages and disadvantages follow :

1. Copper Sulfate

Copper sulfate pentahydrate is the oldest molluscicide in use. It is highly soluble in water and can be added to an infested watercourse in the form of powder, crystals or solutions. Its use as a molluscicide suffers several disadvantages. Due to rapid detoxification, downstream carriage is poor. According to Amin (1972) *Biomphalaria* mortality was only 18% and *Bulinus* mortality 87% only, 3 km downstream from the point of application by drip technique. Although laboratory evaluations of snails against copper ion indicate that molluscicidal dosages are not piscicidal, field dosage requirements are 20 or more times greater and fish readily succumb (Chu et al., 1968).

The use of copper sulfate in quantity is now limited to Egypt, the Sudan and the Middle East. Its basic advantage is the low cost. In many areas it has been found too ineffective for major use (Ritchie & Malek, 1969).

2. Sodium Pentachlorophenate

Sodium pentachlorophenate (NaPCP) has been in use as a molluscicide since 1948. It suppresses egg laying at relatively low concentrations (Olivier & Hoskins, 1960).

Several severe disadvantages of NaPCP renders its present use unattractive. Relatively massive dosages must be used to achieve adequate snail control. Fish and other non-target biota suffer as a consequence. NaPCP presents a high risk of intoxication to those handling it (WHO, 1965).

3. Niclosamide (Bayluscide)

Niclosamide, 5,2'-dichloro-4'-nitrosalicylanilide, is at least 10 times more active than sodium pentachlorophenate (Gönnert & Schraufstatter, 1959). It was first formulated as a 70% wettable powder of the ethanolamine salt, and later a 25% emulsifiable concentrate became available. 2-aminoethanol salt of niclosamide or bay-

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luscide has been extensively evaluated against host snails for the three major forms of schistosomiasis under laboratory and field conditions. All stages of the snails are affected and the ovicidal quality is high.

Bayluscide can be readily dispensed by constant flow devices (Shiff et al., 1973) meter and pump technique (Da-wood et al., 1965) power spraying and even by air. Downstream transmission is good (Shiff et al., 1973).

Bayluscide suffers a number of disadvantages. It is attacked and decomposed by various microorganisms (Etges et al., 1969), effectiveness is a function of pH (Meredith & Meredith, 1971), with increasing loss in toxicity as the pH drops below 7.2 (Meredith, 1971). Bayluscide is very toxic to fish (Marking & Hogan, 1967).

4. Trifenmorph

Trifenmorph (N-tritylmorpholine, Frescon, NL8008) shows considerable promise in snail control. Molluscicidal quality under alkaline pH is generally higher than that of the niclosamide salts and trifenmorph is less hazardous to fish and other non-target biota. Dispensal of available formulations is relatively easy.

Disadvantages exist. Dosage requirements are too high for competitiveness with NaPCP and yurimin in amphibious snail control (Yasuraoka, et al., 1969). Frescon hydrolyses in water to the inactive carbinol, the rate increasing with decreasing pH (Ogersby, 1971). It is neither ovicidal (Meyling et al., 1966) or cercaricidal (Crossland, 1969). Downstream carriage is not as good as that observed with other molluscicides (Berrios-Duran et al., 1968).

5. Other Molluscicides

A number of molluscicides of vegetable origin have been discovered and investigated. Herbicides and larvicides have been evaluated as potential molluscicides. These include various carbamates, acrolein, pasaquat, diquat, 2,4-D amine, lindane, fenthion, DDT and malathion.

Yurimin (3,5-dibromo-4-hydroxy-4-nitrobenzene) compares favorably with NaPCP for *Oncomelania* control. Unlike NaPCP it is stable against UV radiation. Yurimin is piscicidal at molluscicidal dosages. But it has low mammalian toxicity and is judged to be safe to handle.

6. Experimental Molluscicides

A number of experimental molluscicides which are incorporable in controlled release elastomeric matrices have also been evaluated in the conventional sense.

a) Triphenyl lead acetate (TPLA)

Hopf and his coworkers (1967) demonstrated that TPLA was molluscicidal at practical dosages under laboratory conditions. Field evaluation at approximately 0.5 ppm showed good snail control. No evidence of dead fish or amphibia or signs of phytotoxicity were observed in the field tests.

b) DS-2787

DS-2787 (2,4,5,6-tetrachloroisophthalonitrile) is a commercially available fungicide and it has considerable potential as a molluscicide. Adult *B. glabrata* are readily destroyed at dosages of 10-20 ppm (Cardarelli, 1973).

c) Organotins

Organotins with the general formula R_2-Sn-X , where R is an alkyl or aryl group

and X is a functional group such as acetate, oxide, hydroxide or chloride were first examined by Hopf and Müller (1962). Compound codes are as follows :

TBTO bis(Tri-n-butyltin) oxide
 TBTA tri-n-butyltin acetate
 TPTO bis(tri-n-propyltin) oxide
 TPTA triphenyltin acetate
 TBTPC tributyltin pentachlorophenolate

TBTC tributyltin chloride
 TBTS bis(tri-n-butyltin) sulfide
 TBTR tributyltin resinolate

Deschiens et al. (1966) indicated that snail control in small ponds could be achieved at 0.015 ppm TBTO in 3-6 day exposure with no effect on fish.

A limited number of field tests have been performed. In downstream carriage test Berrios-Duran et al. (1968) showed that TBTO applied at 1 ppm for 6 hr was almost as effective as niclosamide against *B. glabrata*.

TABLE 1. Results of short distance field screening tests of molluscicides

Molluscicide	Application time × Conc. (hr × ppm)	Mortality of Laboratory — Reared Snails Exposure Distance (meters)				
		-5m*	30m	1050m	1375m	1540m
Niclosamide	1 × 1	0	77	77	12	—
	1 × 2	5	100	92	70	—
	1 × 3	0	100	100	100	39
	2 × 3	0	100	100	100	100
Frescon	1 × 0.5	0	100	78	15	—
	1 × 1	0	90	100	0	—
	1 × 2	0	100	100	95	—
	2 × 1	0	100	100	90	—
TBTO	6 × 0.25	0	100	43	0	—
	6 × 0.5	0	95	80	70	—
	6 × 1	0	100	100	100	100

(*) 5 m upstream from application point.

Controlled Release Systems

Cardarelli was the first to extend the concept of controlled release of the antifouling materials to snail control. Formulations releasing TBTO, TBTS and TBTA were evaluated against *Helisoma Trivolvis* and excellent mortality rates noted. Berrios-Duran & Ritchie (1968)

examined Cardarelli's antifouling rubber pellets and found them to remain molluscicidal after daily washings over an 18 week period. Long-term laboratory bioassays on controlled release TBTO, TBTR, TBTS and TBTO/Bayluscide mixes were performed by Hopf & Goll (1970). They noted that several formulations remained active over a 26 month period. They also

observed that formulation and vulcanization conditions influenced molluscicidal longevity.

DaSouza & Paulini (1969) evaluated five TBTO formulations and one slow release bayluscide formulation in laboratory and field tests. Both pools and drainage ditches were used as test environments over a 4 month exposure period. Pool tests showed 100% snail mortality. Drainage ditch evaluations, even with flowing water, showed a continuous reduction in living snail populations.

Lack of data concerning the environmental impact and mammalian toxicity of organotin led to the incorporation of a conventional control agent, bayluscide, in chloroprene and other matrices (Cardarelli, 1968). Controlled release is well

confirmed and longevity half-lives in excess of 2 years are predictable. Mammalian toxicity and phytotoxicity are low. The human allergic reaction to powdered bayluscide is not evident after the material is incorporated in rubber.

The basic slow release bayluscide materials are shown in Table 2. The master recipe is as follows:

Ingredient	Formulation parts
Neoprene NRT	100
Zinc Oxide	5
Magnesium Oxide	4
FEF Black	15
PBNA ¹	2
MBT ²	1
Lauric Acid	3

TABLE 2. Slow release Bayluscide (Ethanolamine salt of niclosamide) compounds

Code	Bayluscide Concentration	Loss Rate (Average)	
		Loss/in ² -hr	Loss/g-hr
1121A	5.8%	—	—
1121B	7.1%	3.6 µg	1.44 µg
1121C	10.3%	—	—
1121D	13.4%	7.0 µg	2.80 µg
1121E	18.9%	8.9 µg	3.56 µg
1121F	27.8%	10.5 µg	4.20 µg
1121G	35.0%	39.0 µg	15.60 µg
1121H	43.5%	51.2 µg	20.48 µg

Loss rate curves were plotted over a prolonged laboratory immersion test with periodic sampling and bayluscide determination by the method of Struffe (1960, 1962). The results indicate that an increase in active agent loading by 1/5 parts causes loss rate to increase by almost a factor of 4.

Attempts at incorporation of trifen-

1. Phenyl-B-naphthylamine
2. Mercaptobenzothiazole

morph (Frescon) in a long term controlled release system have not been overly successful to date (Cardarelli, 1974a). The best achievement has been with a 20% active loading in a synthetic natural rubber base. This material provided a 97% mortality in a 10 day bioassay after an initial 215 day water soaking (with periodic water changes) period.

Copper sulfate monohydrate has been incorporated in rubber matrices by compounding and vulcanization (Cardarelli, 1974b; Walker & Cardarelli, 1973). Vulcanization conditions have little effect on loss rate per se, although proper curing retards matrix degradation and enhances the strength properties of the binding element.

Controlled release copper sulfate formulations exhibit typical leach type loss curves. Loss is proportional to exposed surface area. It is also observed that the pH of the water affects the rate of agent release.

Equations have been derived to correlate the matrix characteristics and the nature of the molluscicide and the diffusion rate (Kanakkanatt, 1971, 1972). Diffusion coefficients of various molluscicides determined by sorption and desorption techniques agreed with those predicted by the equations. Determination of water absorption indicated a decrease in water absorption by rubber containing hydrophobic molluscicides.

TBTO reacts with various compounding additives, especially lauric acid and sulfur bearing curatives, in neoprene formulations; and also reacts directly with the polymer giving a rise in the degree of cross-linking (Kanakkanatt, 1972).

The dependence of the diffusion coefficient on temperature and carbon black particle size has been studied. The diffusion coefficient increases with rising temperature and decreases with carbon black content. The particle size apparently has little effect.

In the elastomer the influence of carbon black on viscoelastic properties depends upon several factors; degree of dispersion, surface chemistry and morphological parameters such as size distribution

of the particles. In a rubber carbon black system the rubber that fills the void spaces in a carbon black aggregate is occluded and immobilized, according to theory, and as such acts as a filler rather than as part of the deformable matrix (Medalia, 1972). Other additives can be absorbed by the polymer or react with it (Carr, 1974). The resultant «stabilizing» effect tends to increase diffusion path length thus decreasing diffusion rate.

Solubility of the molluscicide in the elastomer is crucial for long term controlled release utilizing the diffusion-dissolution method. For instance TBTO is soluble in the nitrile fraction of the acrylonitrile polymer but has very low or no solubility in the acrylic portion.

In testing for ovicidal properties 24 hr egg clutches were exposed to various organotin/elastomer concentrations and development monitored. Gastrula stage was destroyed after a prolonged blastula period.

Dr. Santos (1975) and his colleagues screened several organotin controlled release materials in the laboratory against *Oncomelania quadrasi*. The floating TBTF formulation manufactured by the Creative Biology Laboratory provided an LD₅₀ of 46 ppm in 48 hr exposures.

Microenvironmental Bioassay

A useful intermediate step between laboratory bioassay and field evaluation is a microenvironmental examination of the candidate controlled release molluscicide. In test microenvironments created by Cardarelli (1974b,c) a standard soil mixture was used (organic top soil, peat moss and sand), limestone chips to provide calcium, growing aquatic plants, and *Lebistes reticulatus* as a representative non-target fish along with *B. glabrata* as the target mollusc.

Although microenvironmental evaluations indicate that controlled release organotin molluscicides can be used to control snails without untoward piscicidal effects, it must be noted that the test environment changes day by day in chemical and biological character due to the presence and interaction of snails and fish; and the non-target biota cannot escape the proximity of a toxic pellet. Both conditions would likely be absent under field conditions.

Field Evaluation

The initial small field evaluations were conducted in three pond sites, two drainage canals, one well, one pit and one tank in Brazil. Sites showing 100% mortality were periodically recharged with known numbers of viable snails. Results indicated that at dosage levels 50 ppm to 200 ppm gave control for at least a year in still water (Castleton, 1974a,b). Mortality in flowing water systems was 100% for several months but partial repopulation eventually was noted.

Pond tests in Iran provided an LT_{75} of 37 days at 50 ppm dosage and a LT_{100} of 37 days at 90 ppm pellet dosage (Mansouri, 1975).

Elaborate field evaluations have been conducted in Rhodesia. Some irrigation systems restrict the hazard of schistosomiasis transmission to particular structures. In the Middle Sabi scheme snail breeding is generally found in concrete offtake sumps along the main canal. By painting such sumps with TBTO loaded antifouling paint snail control was achieved for 12 months (Shiff, 1974).

In a farm reservoir (coldstream dam) 90 m of a 950 m shoreline were treated with NOFOUL™ (a slow release com-

pound containing 6% TBTO). Strips of 10 cm length were laid parallel through the vegetation near the shoreline. Snail population fell rapidly in the treated area and slowly in the contiguous untreated areas (Shiff, 1974). No fish or frog mortality was noted.

Several small lakes at Belgownie were treated with pellets. Examination of the application sites after 7 months showed the following: No organotin was detected in water taken from the surface or from the bottom of the treatment site. Bottom water samples contaminated with mud showed 0.18 ppm organotin. Mud scraped off submerged pellets and analyzed for organotin showed 0.09-5.07 ppm concentrations. Pellets removed after 7 months immersion contained 1.28% tin compared to 2.15% tin in unimmersed controls (Shiff & Yiannakis, 1975). Thus it is implied, since snail control occurred in the treated areas, that the TBTO released from the pellet remains in the bottom mud. This suggests that snails succumb through browsing on the muddy bottom.

Rothbury Dam (480 m shoreline) was treated with TBTF containing pellets and a rapid decline in snail population noted (Shiff, 1974). To assess the effects on the biotope, samples of bottom mud were taken from treated and untreated sections of Rothbury Dam. No detectable differences in acasina, ostracoda, chironomidae, other insecta and oligochaeta were noted.

Gilbert et al. (1973) formulated several TBTO/asphalt, and TBTO/SBR rubber compounds containing 17% to 20% TBTO. Molluscicidal activity persisted for over 18 months in several of eight field tests conducted. Application was made to pits, drainage ditches, a concrete tank, an irrigation ditch and various marsh sites in

Brazil. In general, good snail control was achieved where the water bodies were essentially static and insufficient control where appreciable flow occurs. It is also reported that immersion in mud and exposure to sunlight did not affect the biocidal activity of the pelletized formulations, and that TBTO apparently acts accumulatively in snails.

Upatham (1975) has shown that the use of controlled release TBTO pellets in a ravine containing flowing water will drastically reduce snail populations.

At this time three controlled release molluscicides are commercially available for field investigation and control programmes. BioMet SRM™, a 6% TBTO in biodegradable natural rubber can be secured from the M & T Chemical Co., Inc., Rahway, New Jersey, U.S.A. Incracide E-51, a 50% copper sulfate monohydrate formulation, is available from the International Copper Research Association, New York, N.Y., U.S.A. and CBL-9B, a 20% TBTF material, can be requested from the Creative Biology Laboratory, Inc., Barberton, Ohio, U.S.A.

Conclusions

Several controlled release molluscicide materials have demonstrated efficacy under field test conditions. Commercially available BIOMET-SRM and INCRACIDE E-51 are safer to handle and have much less environmental impact than is seen with copper sulfate applied conventionally, bayluscide and the pentachlorophenates. Since snail destruction is achieved through chronic intoxication only ultralow toxicant concentrations are necessary. Approximately one-tenth the amount of copper ion is used if the controlled release method is employed. Since TBTO is not used as a conventional agent its ecological advantage cannot be direct-

ly computed. But compared to bayluscide the quantity of TBTO necessary is 1/8 to 1/30 the amount of bayluscide that is conventionally used. Slow release copper should provide a 6 month or better release and the slow release organotins 2 years or better.

Another factor that cannot be easily assessed is the end result arising from the use of conventional and controlled release materials. The objective is to interrupt the transmission cycle. Continuous low level intoxication of the watercourse means that repopulation through migration of snail cannot satisfactorily occur. In the conventional treatment with bayluscide, NaPCP, etc. intoxication lasts for a few days to perhaps 2 weeks. At the end of this period repopulation commences and the schistosomiasis transmission cycle is reestablished within a number of months. BIOMET-SRM should provide an approximate 27 month transmission interruption and INCRACIDE E-51 a 10 month interruption per treatment — provided that the pellets, granules, cords, sheets or whatever form is used remain where placed. Exact results of silting over, current, and external interference with the treatment site cannot be predicted.

Extremely long term controlled release methods are under investigation. Controlled release elastomers can be produced in any size or shape. Concrete irrigation canals, weirs, sumps and so on can be lined with sheet material that will release the active agent for several years — and through refillable systems this can be extended to 20 or more years. A controlled release membrane laminated to a highly loaded reservoir layer will permit a significant extension of release life.

In the refillable system a hollow rubber tube is molded onto a toxic sheet stock containing a wicking fabric — both cotton

and rayon work nicely with TBTO. Liquid in the reservoir is conveyed by the wick and dispensed throughout the sheet. TBTO movement in rayon is several inches per day. Thus, as the sheet material slowly depletes, it is continuously refilled from the incorporated reservoir. The re-

servoir can be refilled once every 3 to 5 years or so. A lifetime of 20 or more years can be envisioned — provided that the toxicant and the rubber sheet do not undergo chemical or photodegradation of a nature that detoxifies or substantially alters the diffusion rate.

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EVALUATION OF CONVENTIONAL AND SLOW-RELEASE FORMULATIONS OF MOLLUSCICIDES AGAINST *BIOMPHALARIA GLABRATA*

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In an effort to develop more efficient molluscicides for controlling *Biomphalaria glabrata*, the intermediate snail host of *Schistosoma mansoni* in Puerto Rico, a laboratory evaluation programme was begun in 1968 at the Center for Disease Control laboratories in Savannah, Georgia. In previous work at the Center for Disease Control laboratories in San Juan, Puerto Rico, Jobins & Unrau (1967) conducted both laboratory and field evaluations of 28 chemicals against this snail species. Results obtained in the laboratory phase of this development effort are presented in the present report. The field studies continued in Puerto Rico on compounds showing promise in laboratory tests conducted at Savannah.

Methods

Snail Rearing

B. glabrata stock were obtained from San Juan and placed in maternity aquaria for egg deposition (Fig. 1). Air stones were used for aeration and plastic strips placed in the aquaria for egg collection. The snails were fed lettuce for food as needed and eggs were collected twice weekly for placing in 150-gallon rearing tanks which were divided by screen baskets (Fig. 2). Approximately 1500 eggs were placed in each basket for rearing. Lettuce was also used for feeding snails

in rearing tanks and young-mature, 9-week-old snails (9-13 mm in size) were harvested for testing. The flow-through water system was maintained at 26.5°C.

Molluscicide Testing (LC₅₀ determinations)

Harvested snails were exposed for 6 hr to ethanol solutions of candidate molluscicides introduced into 2 liters of water (Fig. 3). A concentration series of 2, 1, 0.5, 0.25, and 0.125 ppm was used. When compounds tested were ineffective at the 2-ppm level, higher concentrations were employed if the compound was known to have a high degree of safety to non-target organisms or had other desirable properties. Each concentration was replicated 9 times using 10 snails for each replicate. Bayluscide served as the standard. Ethanol-water and water checks were employed. During the exposure period, reactions such as bleeding, retraction, tendency to extend from the shell, etc., were recorded every 2 hr. After exposure, the snails were removed from the treated water, rinsed, placed in fresh water, fed, and held for 24-hr mortality determinations.

Molluscicide Testing (slow-release formulations)

Polyvinyl chloride (PVC) formulations containing 10, 20, 30, and 40 percent

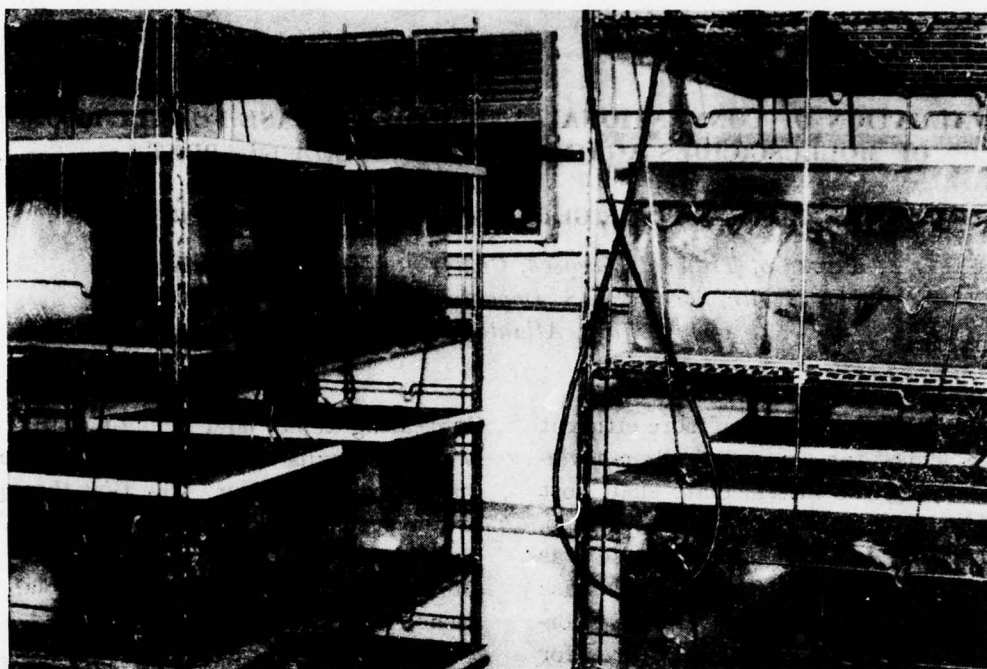


Fig. 1. Maternity aquaria for egg deposition.

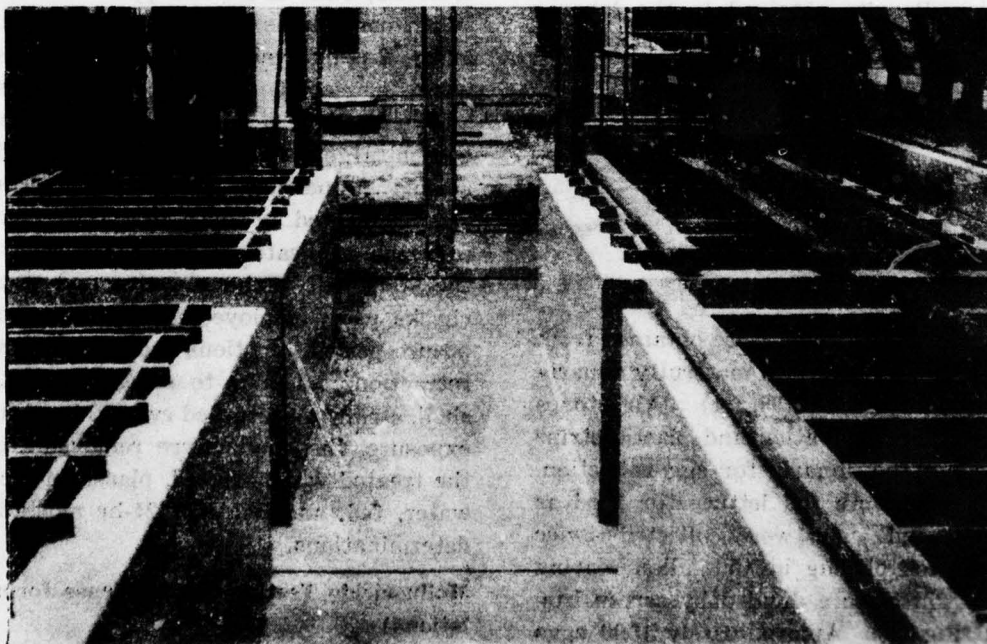


Fig. 2. Rearing tanks.

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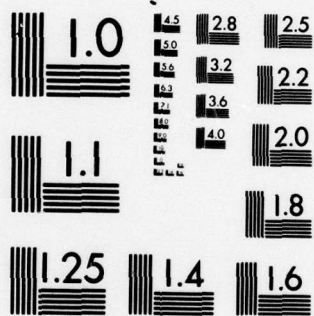
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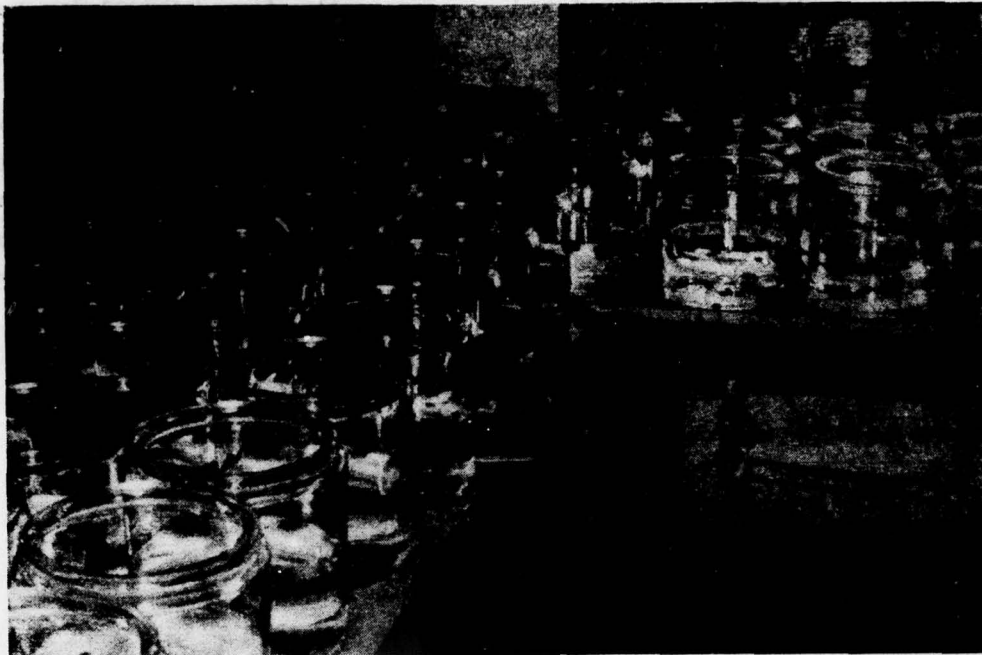


Fig. 3. Provision jars used in molluscicide tests.

Bayluscide were prepared by adding an appropriate amount of Bayluscide to a mixture of equal parts of polyvinyl chloride powder and dioctyl phthalate. The mixtures were poured into flat-bottomed glass vessels and heated at 100°C in a well-ventilated oven to form solid sheets about 1/8-inch thick. In previous work with slow-release formulations, Miles & Woehst (1969) found that addition of a surfactant improved the release rate of Abate formulated with PVC. In order to determine if a surfactant would enhance the release of Bayluscide from PVC, formulations containing 10-40% Bayluscide were prepared with the addition of 10% Tween-80. Chloroprene rubber formulations were furnished by the B.F. Goodrich Rubber Company.*

PVC formulations of 10, 20, 30, and 40% Bayluscide and 10, 20, 30, and 40% Bayluscide plus 10% Tween-80 were cut and weighed out into samples of 0.1, 0.25, 0.5, 1.0, 2.0, and 4.0 grams. Chloroprene rubber formulations of 5.8, 7.1, 10.3, 13.4, 18.9, 35.0, and 43.5% were cut and weighed into sample sizes, also of from 0.1 to 4.0 grams.

Samples were placed in provision jars with 2 liters of water. Initial tests were done on the day of treatment and bi-weekly tests were done through week 14, after which tests were done every 4 weeks through week 36. From week 36 through 56 tests were done only with 10% PVC samples and 13.4% chloroprene rubber samples. Tween-80-water, ethanol-water,

* Use of trade names and commercial sources is for identification only and does not constitute endorsement by the Public Health Service or by the U.S. Department of Health, Education, and Welfare.

and water checks were employed and technical Bayluscide at the 0.5-ppm level was used as a standard. Evaluations were the same as in LC₅₀ determinations. Before each test, water was returned to the 2-liter level.

Chemical Analyses

Samples of water were taken from the jars treated with PVC and chloro-

prene rubber formulations 1 day and 3 days after treatment. The jars were sampled thereafter at weekly intervals. The samples were analyzed by the method of Farrington (1962). The samples were extracted with chloroform and the concentration was determined spectrophotometrically after development of color by the addition of ethanolamine.

Materials

Common or proprietary name

Chemical designation

Frescon

N-trityl morpholine

Bayluscide

ethanolamine salt of 5,2'-dichloro-4'-nitrosalicylanalide

copper—organic 16.0%

copper sulfate

copper—organic 16.2%

copper sulfate

copper—organic 27.6%

copper sulfate

copper—inorganic-fixed 13.8%

copper sulfate

copper—inorganic-fixed 21.3%

copper sulfate

tributyl lead acetate

same

triphenyl lead chloride

same

triphenyl lead acetate

same

Dowco 212-1

confidential

Dowco 215-2

confidential

Dowco 216-2

confidential

Pennsalt TD-5032

confidential

Eli Lilly 153

confidential

chlorpyrifos

0,0-diethyl 0-(3,5,6-trichloro-2-pyridyl) phosphorothioate

Akton

0,0-dimethyl 0-[2-chloro-1-(2,5-dichlorophenyl)vinyl] phosphorothioate

Dimethoate

0,0-dimethyl S-(N-methylcarbamoylmethyl) phosphorodithioate

Abate

0,0-dimethyl phosphorothioate 0,0-diester with 4,4-thiodiphenol

chlorinated levulinic acid

same

hexachlorodemethylsulfone

same

potassium azide

same

Results

LC₉₀ Determinations

Results of these tests are summarized in Table 1. Four of these formulations gave an LC₉₀ of 0.5 ppm or less. Four highly effective organophosphorous mosquito larvicides were found to be completely ineffective against 2.0-ppm dosage level. Five copper and 3 lead compounds were effective at the 1.0-8.0-ppm dosage level. The remaining 8 compounds required 4.0 ppm or greater to produce effective kills.

TABLE 1. 24-hr LC₉₀ of *Biomphalaria glabrata* exposed for 6 hr

Candidate material	LC ₉₀ (ppm)
Frescon	0.125
Bayluscide (technical)	0.25
Bayluscide (e.c.)*	0.25
Bayluscide (granules)	0.50
Copper — organic 16.0%	2.0
Copper — organic 16.2%	2.0
Copper — organic 27.6%	2.0
Copper — inorganic-fixed 13.8%	2.5
Copper — inorganic-fixed 21.3%	> 2.5
Tributyl lead acetate (technical)	1.0
Triphenyl lead chloride (technical)	8.0
Triphenyl lead acetate (technical)	8.0
Dowco 212-1 (technical)	2.0
Dowco 215-2 (technical)	2.0
Dowco 216-2 (technical)	2.0
Pennsalt TD-5032 (technical)	2.0
Eli Lilly 153 (technical)	15.0
Dursban (technical)	> 2.0
Akton (technical)	> 2.0
Dimethoate (e.c.)	> 4.0
Abate (e.c.)	> 4.0
Chlorinated levulinic acid (technical)	> 4
Hexachlorodimethylsulfone (technical)	> 8
Potassium azide (granules)	> 200

(*) emulsifiable concentrate

Slow-Release Formulations

All samples of PVC formulations prepared with Tween-80 gave a 100% kill from the first week through the 36th week of the tests at which time the tests

were terminated. In the case of the PVC samples prepared without surfactant, the smallest sample (0.1 g) of the 10% formulation gave 90% or better kill from the first through the 40th week of the test. Larger samples (0.25-4.0 g) of the 10% formulation gave a 100% kill through 56 weeks. All samples of higher concentrations of Bayluscide (10-40%) gave complete kill of the snails for 36 weeks when the tests were terminated. The 0.5-ppm Bayluscide standard was effective for only 2 weeks. Tween-80-water, ethanol-water, and water checks did not produce snail kill.

The small samples (0.1 and 0.25 g) of the low loadings (5.8 and 7.1%) of Bayluscide in chloroprene rubber were ineffective through week 14 of the test, and tests on these samples were terminated. The smallest (0.1 g) samples of the 10.3 and 13.4% formulations were also ineffective through 14 weeks. The larger samples (0.5 and 1.0 g) of the formulations containing 5.8 to 13.4% Bayluscide were ineffective initially, but began to kill at 2-4 weeks. With the exception of the 0.1-g sample, all samples of the 13.4% formulation gave effective kill through 56 weeks of tests. Samples with higher loadings of Bayluscide were also effective for the duration of the tests; however, tests on these samples were terminated after 36 weeks.

The jars containing the PVC and chloroprene rubber formulations were monitored by chemical analyses for a period of 10 weeks. All formulations released measurable concentrations of Bayluscide within one day. Formulations of PVC and rubber which were prepared with high concentrations of Bayluscide produced proportionately higher concentrations of the molluscicide in water than those formulated with lower concentrations. The rubber formulations held the

Bayluscide more tightly than did the PVC formulations. The rubber formulations released the toxicant at a slower rate and reached equilibrium at a lower dosage level than did comparable PVC formulations. PVC formulations containing Tween-80 exhibited a high initial release

rate with a maximum release at about one week; however, after 3-4 weeks these formulations established equilibrium at about the same concentrations as those containing equal amounts of Bayluscide with no surfactant. A typical release pattern is shown in Fig. 4.

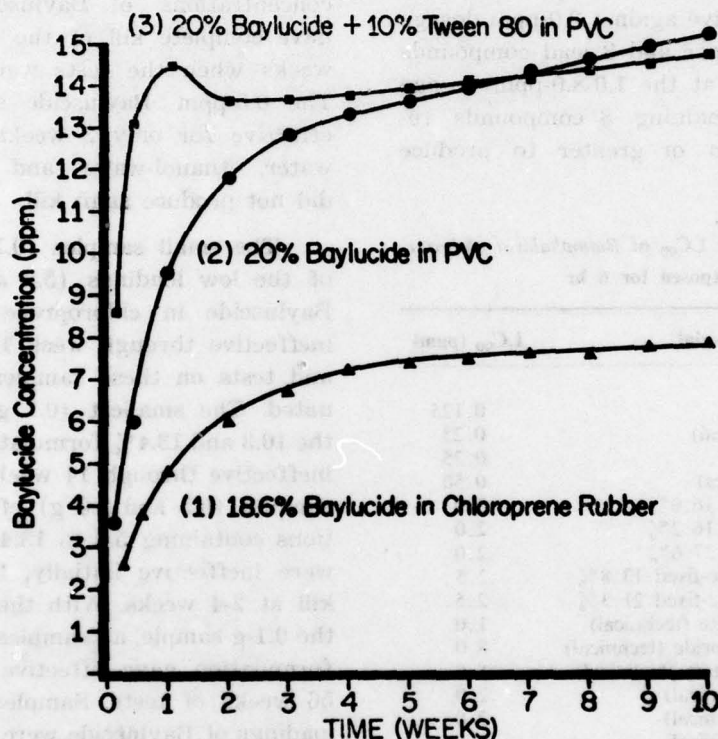


Fig. 4. Patterns of release of Bayluscide into water by rubber and polyvinyl chloride (PVC) formulations. Two-liter jars of water were treated with: (1) 2 g chloroprene rubber containing 18.6% Bayluscide; (2) 1.86 g PVC containing 20% Bayluscide; or (3) 1.86 g PVC containing 20% Bayluscide plus 10% Tween-80

Summary and Conclusions

Four of the 24 conventional candidate molluscicides formulations tested in the laboratory against 9-week-old *Biomphalaria glabrata* gave an LC_{50} of 0.5 ppm or less. These were Frescon and three Bayluscide formulations. The granular formulation of Bayluscide was somewhat less toxic than the technical and emulsifiable concentrate formulations, probably due to some binding of the compound by

the granules. Five copper and 3 lead compounds were effective at the 1.0-8.0-ppm dosage level. These compounds would unfortunately be unacceptable for widespread use due to recent environmental restrictions placed on heavy metals. Four organophosphorous insecticides and the remainder of the compounds studied required from 2->200 ppm for effective molluscicidal activity, and therefore would not be suitable for further testing.

Slow-release formulations of Bayluscide in polyvinyl chloride and chloroprene rubber were biologically effective for up to one year. Most PVC formulations were effective on treatment day and through the test period. Some chloroprene rubber formulations did not release sufficient toxicant to be effective until up to 4 weeks after treatment. These formulations show promise for further field testing.

Both PVC and chloroprene rubber proved to be satisfactory matrices for slow-release formulations of Bayluscide. Chloroprene rubber released the molluscicide at a slower rate than PVC formulations prepared with comparable loadings of active ingredient. When a surfactant was added to the PVC formulations, the initial rate of release was increased; however, after 3-4 weeks, the rate was reduced to the level observed in similar formulations prepared without surfactant.

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SCREENING OF MOLLUSCIDAL ACTION AGAINST *BIOMPHALARIA ALEXANDRINA*

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In view of the importance of snail control in the control of schistosomiasis, a series of compounds were tested for their molluscicidal potency against laboratory bred *Biomphalaria* snails kept under standard laboratory conditions. The snails were bred with due attention paid to diet, the presence of inorganic salts and turbidity, as discussed by Harrison & Farina (1965), Harrison et al. (1966) and Souza & Paulini (1969).

The comparative investigation included 5 recognized molluscicides, various chlorinated carbons, organophosphorous and carbamate insecticides and a series of surface active agents and larvicides such as amines, alcohols, alkaloids and phenols.

An attempt was also made to study the mode of action of potent molluscicides in relation to catalase and peroxidase activity in these snails.

Materials and Methods

1. Laboratory breeding of *Biomphalaria alexandrina*

Adult snails were freshly collected from the vicinity of Alexandria at Kafr El Dawar. They were reared at a constant temperature of $25 \pm 2^\circ\text{C}$ in glass aquaria, each containing 6 liters of water and 10 adult snails. The water was taken from Mahmoudia canal and was stored for

decantation to prevent any deleterious effect of turbid water on the egg capsules.

2. Analysis of water samples

Water samples taken from Mahmoudia canal were analysed according to the methods described by Cumming & Kay (1942).

3. Screening method for testing molluscicidal activity

The procedure followed for measuring the molluscicidal activity of the chemical compounds tested against adult snails was based on the provisional method recommended by WHO (1961, 1965a). Snails were exposed to the chemicals for 24 hr and allowed a 24 hr recovery period before testing.

4. Chemical compounds tested

a) Specific molluscicides

- 1) Copper sulphate, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ crystals.
- 2) Sodium pentachlorophenate, (NaPCP) technical, 80%.
- 3) Niclosamide (Bayluscide), (2',5-dichloro-4'-nitro salicyl anilide) wettable powder 70%, (Bayer).
- 4) Molucid, isobutyl triphenylmethyl amine, (I.C.I.).

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5) Frescon, N - tritylmorpholine.
16.5% emulsifiable concentrate
(E.C.) (Shell).

b) *Chlorinated hydrocarbon insecticides*

1) Endosulfan (Thiodan), technical, pure.

6,7,8,9,10,10-hexachloro - 1,5,5a,6,9,9a-hexahydro-6,9 - methano-,2,4,3-benzodioxathipin-3-oxide.

2) Endrin, technical, pure.

1,2,3,4,10,10-hexachloro-6,7 epoxy-1,4,4a,5,6,7,8,8a - octahydro - 1,4 - endo, endo-5,8-dimethano-naphtalene.

3) DDT, technical, pure.

2,3-bis (p'-chlorophenyl), 1,1,1-trichloroethane.

4) Dieldrin, technical, pure.

1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a - octahydro - 1,4 - endo, exo-5,8-dimethano-naphtalene.

5) Methoxychlor, technical 89.5%.

2,2-bis (p'-methoxyphenyl) 1,1,1-trichloroethane.

6) Heptachlor, technical, pure.

1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene.

7) Lindane, technical, pure.

1,2,3,4,5,6-hexachloro cyclohexane.

8) Toxaphene, technical, pure.

Chlorinated camphene.

c) *Organophosphorous insecticides*

1) Diptrex, technical, pure.

0,0-dimethyl-1-hydroxy-2-trichloro ethyl phosphonate.

2) Dursban, technical 95%.

0,0-diethyl 0-3,5,6 trichloro-2 pyridyl phosphorothioate.

d) *Carbamate insecticides*

1) Matacil, technical, pure.

4-dimethyl-amino m-tolyl-N-dimethyl carbamate.

2) Dimetilan, technical, pure.

2-dimethyl carbamoyl-3-methyl-5-pyrazolyl dimethyl carbamate.

3) CFB, technical, pure.

p-fluorophenyl-N-methyl carbamate.

4) Zectran, technical, pure.

3,5-dimethyl-4-dimethyl amino-phenyl-N-methyl carbamate.

5) Temick, technical, pure.

2-methyl-2-(methylthio) propionaldehyde 0-(methyl carbamoyl) oxime.

e) *Phenols*

p-C₂H₅ (para-ethyl phenol), p-CH₃ (para methyl phenol), p-CH₃O (para methoxy phenol) p-C₂H₅O (para ethoxy phenol), p-OH phenol (hydroquinone), p-NO₂ phenol, p-Cl (p-chloro phenol), p-n-propyl phenol, p-n-isopropylphenol, p-secondary-butyl phenol, p-tertiary-butyl phenol, and naphtalene for comparison with α-naphthol.

f) *Alcohols*

Methanol, ethanol, n-propyl alcohol, isopropyl alcohol, n-butyl alcohol, iso-amyl alcohol, tertiary amyl alcohol, octanol, n-decanol, chloro-ethanol, phenoxy-ethanol, menthol, propylene-glycol, and polyethylene-glycol.

g) *Amines and alkaloids*

Ammonia, ethanol amine, isopropyl amine, diphenyl amine, α -naphthyl amine, aniline, p-methyl aniline, p-nitro aniline, p-amino-benzoic acid, nicotinic acid, pyridine, 2,4,6-trimethyl pyridine, and nicotine sulphate.

5. **Preparation of crude peroxidase and catalase from snail homogenate**

The procedure followed for preparation of crude peroxidase and catalase from snail homogenate was that advocated by Bergmeyer (1963).

6. **Measurement of peroxidase activity**

The method used for measuring peroxidase in the snail extract was, with slight modification, that of Ponting & Josly (1948), i.e., a direct colorimetric measurement of guaiacol oxidation. Absorbencies at 530 m μ were read at 30 sec. intervals at a temperature of 20°C.

7. **Measurement of peroxidase inhibition**

a) *Qualitative test*

The most toxic compounds were tested qualitatively as inhibitors to peroxidase. To the mixture which was used for measuring peroxidase activity 1 ml of each toxic compound was added, and the mixture was incubated for 1 hr. The appearance of a red colour indicates the presence of peroxidase enzyme activity.

b) *Quantitative test*

The quantitative inhibition of peroxidase by hydroquinone, a potent inhibitor, was studied by using different concentrations of the inhibitor; 1 ml of each concentration was incubated for an hour with the reaction mixture. Then the activity of the enzyme in the presence of

hydroquinone was determined as mentioned under peroxidase activity.

8. **Measurement of catalase activity**

The procedure followed for measuring catalase activity was that reported by Saunders (1964).

9. **Measurement of catalase inhibition**

a) *Qualitative test*

The most toxic compounds were tested qualitatively as inhibitors to catalase enzyme: 1 ml of each compound was incubated with 1 ml enzyme preparation for an hour. The former mixture was added to the optimum substrate concentration (0.4 M H₂O₂) at 0°C and watched for the evolution of oxygen, which indicates the presence of catalase enzyme activity.

b) *Quantitative test*

The quantitative inhibition of catalase by the moderately inhibiting hydroquinone was studied, using different concentrations of inhibitor. 1 ml of each concentration was incubated with 1 ml enzyme dilution for an hour. Then the activity in the presence of the inhibitor was determined.

Results and Discussion

1. **Laboratory breeding of *Biomphalaria alexandrina***

Preliminary trials failed to breed these snails under laboratory conditions using tap water, as the snails, although they survived, did not lay eggs in it. When tap water was replaced by water from the Mahmoudia canal, the snails began to lay eggs. Chemical analysis of water samples showed that Mahmoudia water was rich in calcium content (38-39.45 ppm of CaCO₃) and also contained 8.6-10 ppm of magnesium as pyrophosphate. Thus

the calcium/magnesium ratio is about 4. Such a high ratio of calcium is essential for egg laying, as mentioned by Harrison & Farina (1965).

Statistical analysis showed that there was no significant difference between field and laboratory strains in their susceptibility to molluscicides. This indicated the feasibility of using such a standard laboratory strain for testing molluscicidal toxicity.

Under the conditions prevailing in our aquaria, an average of 2 egg clutches per week per snail were obtained. The egg clutches hatched within 1-2 weeks. The juvenile snails reached 9-10 mm in diameter in 10 weeks and were then sexually mature. The average weight of each snail was 118 mg.

The effect of diet on the egg laying rate was studied. In the egg clutches of the group raised on castor bean leaves which showed a strong yellow colour, the frequency of egg laying was 2 egg clutches per week per snail. When raised

on lettuce and on spinach the average was 2.05 and 3.0 egg clutches per week per snail respectively. The higher average of egg laying in the case of spinach can be attributed to the higher protein content of spinach leaves. Castor bean leaves were chosen as a diet because of their availability all the year round. The laboratory strain of *Biomphalaria* was maintained under normal room conditions of relative humidity and illumination. In winter a heater was used to raise the aquarium temperature to about 25°C and the jars were also exposed to the rays of the sun for 1 or 2 hr daily. Every generation lived for about 3 months.

2. Molluscicidal activity

a) Specific molluscicides

The LC_{50} and LC_{95} values of the molluscicides tested are presented in Table 1, together with their respective slopes and confidence limits. The molar LC_{50} values are included to give a more precise criterion for comparative toxicity (El-Sebae, 1968).

TABLE 1. LC_{50} and LC_{95} values of 5 acknowledged molluscicides against *Biomphalaria alexandrina* after a 24 hr exposure and a 24 hr recovery period.

Compounds	LC_{50} (and 95% confidence limits) (ppm)	LC_{95} (and 95% confidence limits) (ppm)	Slope	Molar $LC_{50} \times 10^7$
Frescon	0.019 (0.017-0.022)	0.034 (0.027-0.041)	6.7	0.57
	0.039 (0.032-0.048)	0.084 (0.062-0.11)	5.0	1.2
Niclosamide (Bayluscide)	0.04 (0.026-0.046)	0.26 (0.14-0.48)	1.9	1.2
NaPCP	0.44 (0.32-0.60)	2.1 (1.18-3.74)	2.9	15.0
Copper sulphate	3.1 (1.55-6.2)	19 (5.93-60.8)	2.1	120.0

Frescon was found to be the most effective, being more than 150 times as potent as copper sulphate. Next came Molucid and Niclosamide and far behind sodium pentachlorophenate and copper sulphate, the least toxic compound.

Frescon had the highest slope for the regression line, which suggests a rapid rate of entry and penetration and might also indicate a rapid toxic action. Frescon and Molucid showed approximately similar slope values, a fact which might imply that these 2 chemical compounds have a similar mode of action. The molecular configuration of the 2 compounds favours such an assumption of similarity.

The trend of relative potency in the present results is similar to those report-

ed in the literature. Shiff & Ward (1966) found Frescon more active against *Biomphalaria pfeifferi* than Molucid and the latter more active than Niclosamide, while Bruaux & Gillet (1961) had reported Niclosamide (Bayluscide) to be more effective against *Biomphalaria* than copper pentachlorophenate and copper sulphate. Paulini et al. (1968), testing Frescon against *Biomphalaria*, had found that a combination with Niclosamide resulted in an additive toxic effect, but that no synergism was obtained.

b) Chlorinated hydrocarbon insecticides

The LC_{50} and LC_{95} values are tabulated in Table 2 with corresponding slopes, confidence limits and molar LC_{50} values. The most active compounds were

TABLE 2. LC_{50} and LC_{95} values of chlorinated hydrocarbon insecticides against *Biomphalaria alexandrina* after a 24 hr exposure and a 24 hr recovery period.

Compounds	LC_{50} (and 95% confidence limits) (ppm)	LC_{95} (and 95% confidence limits) (ppm)	Slope	Molar $LC_{50} \times 10^7$
Toxaphene	0.39 (0.28—0.53)	2.15 (1.16—3.97)	2.2	9.4
Endosulfan	0.4 (0.27—0.59)	2.4 (1.16—4.97)	2.2	9.8
DDT	0.58 (0.52—0.75)	2.7 (1.45—4.99)	2.6	16.0
Lindane	0.78 (0.52—1.17)	5 (1.9—12.8)	2.1	26.0
Dieldrin	0.88 (0.49—1.58)	7.8 (4.06—14.97)	1.7	23.0
Methoxychlor	5.6 (4.59—6.83)	15 (11.3—19.8)	4.1	170.0
Heptachlor	9.4 (7.40—11.94)	25 (16.6—37.5)	4.0	250.0
Endrin	no kill at 10 ppm	—	—	—

Toxaphene, Endosulfan and DDT, followed by Lindane, Dieldrin, Methoxychlor and Heptachlor in descending order. Endrin was not toxic up to a concentration of 10 ppm. Since Dieldrin is the endo-exo analogue of the endo-endo isomer Endrin, this is a clear case of selectivity. A second case of selectivity was revealed between DDT and Methoxychlor. It is also quite interesting to note that Toxaphene and Endosulfan were almost as toxic as the specific molluscicide sodium pentachlorophenate. The relatively low LC_{50} of Toxaphene (0.39 ppm) suggests the possibility of using it in such a dose, which is safe for mammals, as a multipurpose pesticide against insects and snails.

c) Organophosphorous and carbamate insecticides

No significant toxicity was shown by any of the carbamates or organophosphorous insecticides tested up to concentrations of 10 ppm. This lack of toxicity ascertains selectivity and might be due to the relatively high polarity of the tested compounds which might hinder its ability of penetration to induce contact toxicity.

d) Toxicity of phenols

Table 3 presents the LC_{50} , LC_{95} and molar LC_{50} values with their respective slopes for the phenols tested.

TABLE 3. LC_{50} , LC_{95} and molar LC_{50} values of various phenols, alcohols, amines and alkaloids against *Biomphalaria alexandrina* after a 24 hr exposure and a 24 hr recovery period.

Compounds	LC_{50} ppm	LC_{95} ppm	Slope	Molar $LC_{50} \times 10^7$
PHENOLS				
p-chloro-phenol	36.0	88.0	3.95	2700.0
p-OH-phenol (Hydroquinone)	7.0	20.0	3.70	630.0
p-sec.-butyl-phenol	8.0	12.5	9.3	520.0
naphthalene	3.7	7.0	6.15	270.0
ALCOHOLS				
iso-amyl alcohol+1 ppm Tween 20*	72.0	115.0	8.61	8100.0
octanol+1 ppm Tween 20.	33.0	120.0	3.00	2500.0
n-decanol+1 ppm Tween 20.	3.9	13.0	3.2	240.0
AMINES AND ALKALOIDS				
ammonia	88.0	175	5.8	51000.0
iso-propyl-amine	74.0	110	10.9	12000.0
diphenyl-amine	11.5	115	1.7	680.0
α -naphthyl-amine	40.0	100	4.4	2700.0
p-nitro-aniline	36.0	96	4.6	2600.0
2,4,6-trimethylpyridine	150.0	520	2.95	12000.0
nicotine sulphate	36.0	420	1.55	1400.0

(*) a surfactant.

The most toxic compound of the series at the LC_{50} level was hydroquinone (P-OH phenol) followed by p-sec-butyl phenol and then p-chloro-phenol. Due to its higher slope p-sec-butyl-phenol was more toxic at the LC_{95} level than the hydroquinone. The increase in the number of carbon atoms in the molecule might increase the tendency for rapid penetration which can be visualized from high increase in slope for the p-sec-butyl-phenol.

α -naphthol was of very low toxicity at a concentration of 10 ppm. However its precursor, naphthalene, showed a relatively high toxicity which is almost equal to that of the specific molluscicide copper sulphate. The particular higher toxicity of the p-OH-phenol as compared to its isomer m-OH-phenol might be due to the easiness of converting p-OH-phenol to the toxic quinone form.

The higher toxicity of p-chloro-phenol as compared to phenol itself agrees with the results of Nolan et al. (1953), that highly halogenated phenols are active molluscicides. The p-Cl group is an electron attracting group which will confer less polarity, thus reducing the dipole moment and being more favorable for inducing toxicity.

e) Toxicity of alcohols

Structure toxicity relationships were studied against *Biomphalaria alexandrina* using a series of alcohols. Table 3 shows the LC_{50} , LC_{95} and molar LC_{50} values with their slopes. Generally, toxicity increased when increasing the number of C atoms. N-decanol was the most toxic followed by octanol and iso-amyl alcohol.

f) Toxicity of amines and alkaloids

Ammonia and its derivatives were studied so as to follow the relation be-

tween chemical structure and toxicity to snails. The diphenylamine was the most toxic compound followed by p-nitro-aniline, which is equal in toxicity to nicotine sulphate (Table 3). Amines are the parent compounds of some of the recent molluscicides such as Niclosamide (Bayluscide), Molucid and Frescon. Amines are known to be toxic as mosquito larvicides (Mulla, 1967; Mulla & Chandhury, 1968). Hardy (1969) mentioned that nicotine amides were highly toxic to *Australorbis glabratus*.

3. Mode of action of molluscicides

New information is needed so as to furnish a basis for interpreting the toxicity of molluscicides and to suggest their mode of action, as well as to elucidate the mechanism and site of the toxic effect.

Zsolnai (1971) stated that most compounds which inhibit sulfhydryl enzymes were molluscicidal since they were protoplasmic poisons. Little is known on the effect of molluscicides on enzymes in general. Some authors have suggested that Niclosamide is an inhibitor of the enzymes peroxidase and catalase (Nabih & El Wasimi, 1968). Therefore these oxidative enzymes were chosen for more thorough study.

a) Peroxidase activity and inhibition

The presence and activity of peroxidase in total snail homogenate was demonstrated. The occurrence of peroxidase in *Biomphalaria alexandrina*, as determined in the present investigation, corroborates previous results by Saunders (1964), who reported that peroxidase is present in various molluscs. A similar conclusion was made by Nabih & El Wasimi (1968), who found catalase and peroxidase (protoporphyrin enzymes) in *Biom-*

phalaria and *Bulinus* snails. The data prove that the reaction is a first order reaction in which there was a direct proportional increase in rate of reaction by increasing the amount of substrate.

The optimum substrate concentration was calculated at 5-minute intervals as 0.05 M H_2O_2 in total volume.

A qualitative test was carried out to study the effect of 14 toxic compounds on peroxidase activity. Hydroquinone was the only compound to inhibit the enzyme. Therefore, the kinetics of this inhibition were investigated quantitatively. The I_{50} value of hydroquinone to peroxidase activity in snail homogenate after 1 hour of incubation was found to be 6.2×10^{-5} M.

No recorded I_{50} values of such an enzyme system could be traced in the literature for comparison. The only related work was that by Nabih & El Wasimi (1968) who, using phenylene diamine in estimation of peroxidase, concluded, qualitatively, that Niclosamide was an inhibitor of peroxidase. However, Saunders (1964) had criticized this method because phenylene diamine is very sensitive to many other oxidizing agents. The present results did not agree with the qualitative test of Nabih & El Wasimi.

b) Catalase activity and inhibition

The second enzyme system which was explored was the catalase system. Nabih & El Wasimi (1968) stated that catalase was found in *Biomphalaria alexandrina* and in other species of snails. Qualitative tests proved the occurrence of catalase in the total homogenate of snails. Quantitative data also supported the occurrence of the enzyme. The direct proportional increase in velocity of enzymatic reaction with increase in substrate concentration suggests that the biochemical reaction is of the first order type. The

optimum concentration was found to be 0.4 M H_2O_2 .

Comparing kinetic data for both catalase and peroxidase in total snail homogenate it is shown that in snails peroxidase activity is much higher than catalase activity.

	Peroxidase	Catalase
V max	0.1 M/min	5.1×10^{-3} M/min
Km	4.6×10^{-1} M/l	12.3×10^{-2} M/l

where V = velocity of reactions ;

M/min = mole per minute.

K = a constant ; m = Michaelis constant.

The qualitative test revealed that none of the tested compounds could inhibit catalase except hydroquinone, which was proved also to be an inhibitor to peroxidase in snails. The molluscicidal action of hydroquinone might well be due to such as inhibiting effect with respect to peroxidase and catalase. The I_{50} value of hydroquinone for catalase in total snail homogenate was 2.8×10^{-3} M. An I_{50} value of 6.2×10^{-5} M of hydroquinone for peroxidase showed that hydroquinone inhibits peroxidase more highly than catalase. This might reflect certain specific and selective biochemical variations. No data were found in the literature concerning quantitative estimation of catalase enzyme inhibition in snails.

c) Discussion

Saunders (1964) reported that hydroquinone might inhibit lactoperoxidase enzymes. It can be postulated that hydroquinone might form a metallic salt by conjugation with a ferric atom in the center of the protoporphyrin group. This can be supported by the fact that hydroquinone is the only compound of the ben-

zene series known to enter into the Diels-Alder reaction to form adduct ketone complexes with certain sites on enzyme surface (Fieser & Fieser, 1961).

Villirs & Rossouw (1967) concluded that some amides and morpholides were toxic to snails because of a physical interference with the properties of membranes or interfaces within the snail and not, because of any biochemical reaction. Frescon, Niclosamide and Molucid are structurally similar to morpholides and amides respectively. This fact suggests that the mode of toxic action of such highly potent organic molluscicides might be through physical interference with the cell membranes which would hinder their functions and thereby lead to death.

It can be stated in conclusion that :

- our work has confirmed that none of the many compounds screened can compete with the present molluscicides of choice, Frescon and Niclosamide

(Bayluscide), which are particularly recommended because of their low mammalian toxicity (LD_{50} of 1400 mg/kg for Frescon ; 5 g/kg for Niclosamide) (Martin, 1971 ; WHO, 1965b)

- none of the widely used field insecticides can be used for the dual purpose of simultaneous mollusciciding and insecticiding ;
- there exists an inverse effect between molluscicidal activity and surface activity in different organic series including amines, alcohols, phenols and phenol derivatives ;
- the highly potent specific organic molluscicides such as Frescon, Molucid and Niclosamide did not show evidence of being inhibitors of peroxidase or catalase in snail homogenate, although it was reported in the literature that their toxicity is accompanied by reduction in O_2 assumption (Gönnert, 1961).

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THE MOLLUSCICIDAL PROPERTIES OF SUBSTANCES GAINED FROM *AMBROSIA MARITIMA*

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The decline of snail populations is accepted as presumptive evidence of success during antibilharzial work. Despite the recent progress in snail control by synthetic chemicals, none measured up to the standards of an ideal molluscicide due to their toxicity to other aquatic creatures. The search for less dangerous natural molluscicides may offer progress in this field.

A number of plants occurring in various geographical areas have long been known to contain substances toxic to fish and snails. Thus the destructive effect on snails, cercariae and miracidia of extracts from *Balanites aegyptiaca* (Mozley, 1939; Manson-Bahr, 1954), *Sapindus saponaria*, *Swartzia madagascariensis* (Mozley, 1939, 1952) and *Tephrosia vogelli* (Manson-Bahr, 1954) was reported at an early time. The molluscicidal properties of *Phytolacca dodecandra* were determined later (Lemma, 1970). From the berries of the latter, an aglycon similar in structure to oleanic acid was reported as the active constituent of the plant (Baalawy, 1972).

Ambrosia maritima, a herb occurring in the southern districts of Egypt, has also been known for some time for its molluscicidal properties. The active constituents, named Damsin and Ambrosin, which belong to a class of compounds known as «sesquiterpene lactones», were

extracted and characterized over 20 years ago, and a third product, Tribromo-Damsin was synthesized from Damsin (Abu Shady & Soine, 1953). The toxicity of extracts from the leaves and flowering tops of the plant on *Bulinus*, *Biomphalaria* and *Lymnaea* was also investigated by Sherif et al. (1962).

The present study deals with an investigation of the comparative susceptibility of *Biomphalaria alexandrina* and *Bulinus truncatus* to the molluscicidal action of these 3 compounds (compounds I, II and III).

Moreover, Damsin, being the main constituent of the herb, was chosen for detailed studies to determine the effect of time-concentration relationship, pH, sunlight, river-bed mud and storage on its molluscicidal activity.

Materials and Methods

Snails and molluscicidal agents

The two snail intermediate hosts of schistosomiasis in Egypt, *Bulinus truncatus* and *Biomphalaria alexandrina*, were used in this study. They were collected from irrigation canals, located in Giza Governorate that had not been treated with molluscicides. The snails were acclimatized to laboratory conditions for a period of at least 3 months before being used in toxicity tests.

Damsin (I) and Ambrosin (II) were extracted from *Ambrosia maritima* and purified by repeated chromatography. The Tribromo-Damsin (III) was synthesized from Damsin according to Abu-Shady & Soine (1953). The structure of these compounds is shown in Fig. 1.

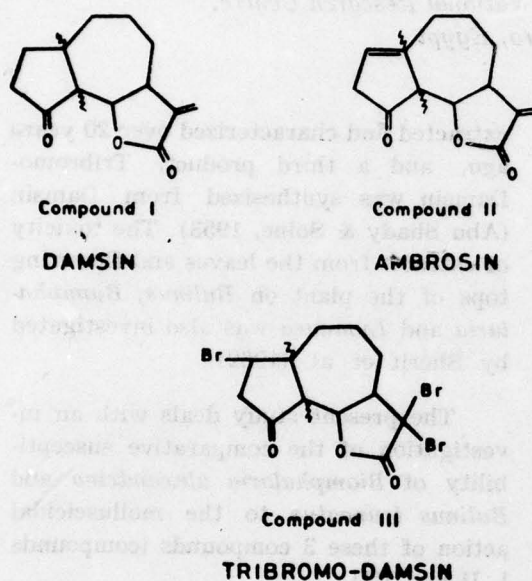


Fig. 1. Molluscicidal agents gained from *Ambrosia maritima*

TABLE 1. Comparative susceptibility of *Biomphalaria alexandrina* and *Bulinus truncatus* to compounds, I, II and III.

Compound	Exposure period (hr)	<i>B. alexandrina</i>		<i>B. truncatus</i>	
		LC ₅₀ *	LC ₉₀	LC ₅₀ *	LC ₉₀
		ppm	ppm	ppm	ppm
I	6	125 (115.6—135.0)	192	66 (62.3—69.8)	84
I	24	6.4 (5.9—6.8)	9.7	7.0 (6.14—7.98)	13.5
II	24	8.0 (7.6—8.4)	10.9	6.0 (5.6—6.4)	8.5
III	24	9.3 (8.5—10.1)	14.5	5.6 (5.2—6.04)	8.2

(*) 95% confidence limits in parentheses.

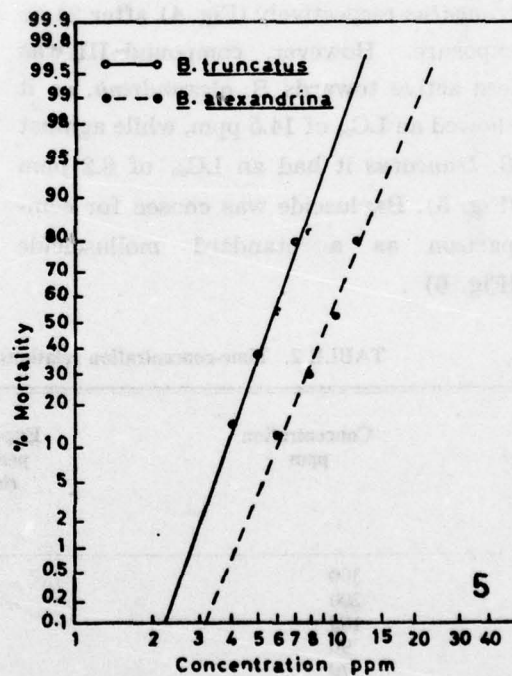
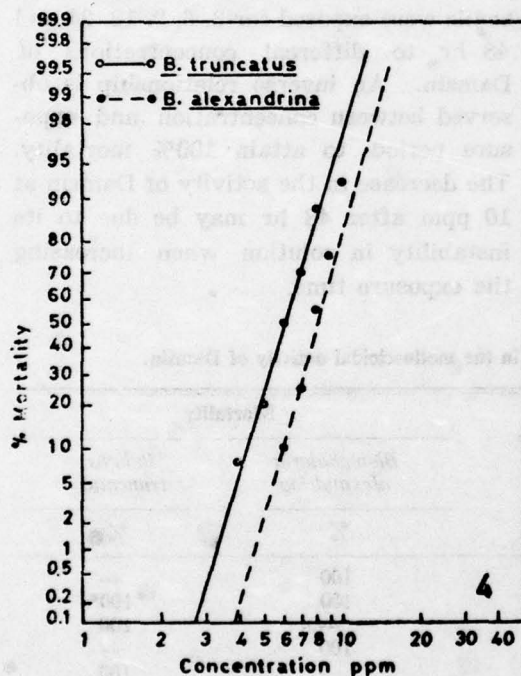
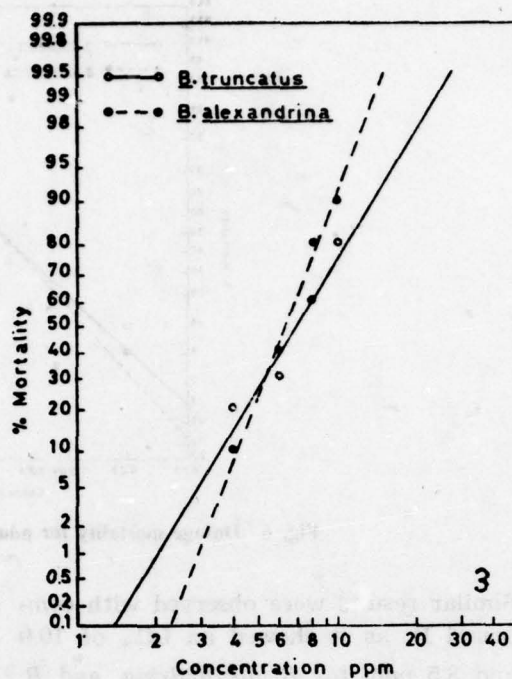
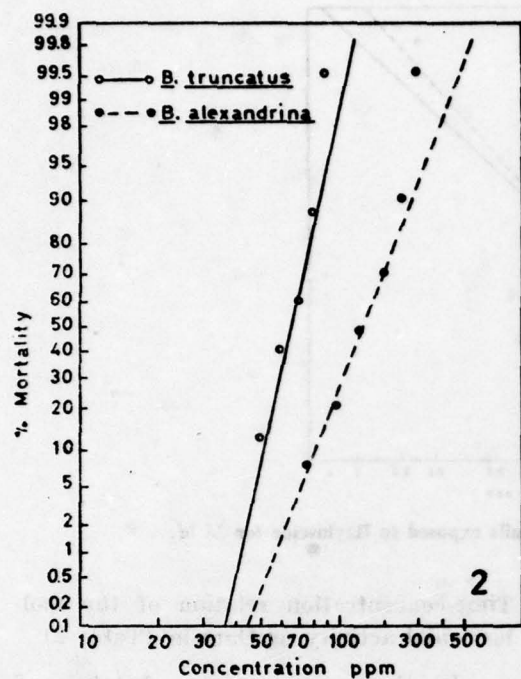
Preparation of molluscicide solutions

Stock solutions of 1000 ppm were freshly prepared on a basis of weight/volume in distilled water. Series of concentrations that permit the computation of LC₅₀ values were prepared. Standard procedures were followed throughout this study (WHO, 1953, 1965). The effect of the three compounds has been expressed in terms of LC₅₀ and LC₉₀ (Litchfield & Wilcoxon, 1949).

Results

Susceptibility of *Biomphalaria alexandrina* and *Bulinus truncatus* to the molluscicidal action of compounds I-III as compared to Bayluscide

From Table 1 it is clear that the two snail types vary in their susceptibility towards the three compounds. Compound I exhibited an LC₉₀ of 192 ppm against *B. alexandrina* and of 84 ppm against *B. truncatus* after 6 hr of exposure (Fig. 2). By increasing the exposure period to 24 hr, the LC₉₀ of compound I dropped to 9.7 and 13.5 ppm respectively (Fig. 3).



Figs. 2-5. Dosage mortality for adult snails exposed as follows:

Fig. 2. to Damsin for 6 hr; Fig. 3, to Damsin for 24 hr; Fig. 4. to Ambrosin for 24 hr; Fig. 5, to Tribromo-Damsin for 24 hr.

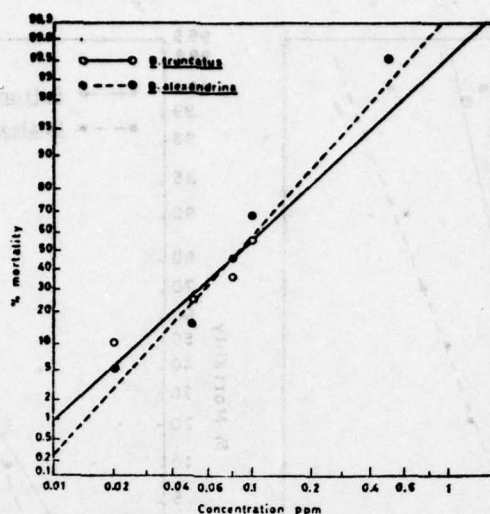


Fig. 6. Dosage mortality for adult snails exposed to Bayluscide for 24 hr.

Similar results were observed with compound II, as it showed an LC_{90} of 10.9 and 8.5 ppm for *B. alexandrina* and *B. truncatus* respectively (Fig. 4) after 24 hr exposure. However, compound III was less active towards *B. alexandrina*, as it showed an LC_{90} of 14.5 ppm, while against *B. truncatus* it had an LC_{90} of 8.2 ppm (Fig. 5). Bayluscide was chosen for comparison as a standard molluscicide (Fig. 6).

Time-concentration relation of the molluscicidal activity of Damsin (Table 2)

In these experiments, batches of snails were exposed for 3, 6, 9, 12, 24 and 48 hr to different concentrations of Damsin. An inverse relationship is observed between concentration and exposure period to attain 100% mortality. The decrease in the activity of Damsin at 10 ppm after 48 hr may be due to its instability in solution when increasing the exposure time.

TABLE 2. Time-concentration relationships in the molluscicidal activity of Damsin.

Concentration ppm	Exposure periods (hr)	Mortality	
		<i>Biomphalaria alexandrina</i>	<i>Bulinus truncatus</i>
		%	%
300	3	100	—
200	6	100	100*
100	6	—	100
90	9	100	—
70	9	—	100
0	12	100	100
15	24	100	100
10	48	40	70

(*) 100% mortality after 3 hr exposure.

TABLE 3. Effect of pH on the molluscicidal potency of Damsin.

pH values	Mortality of snails exposed for 24 hr* to the following concentrations (ppm)											
	<i>Biomphalaria</i>						<i>Bulinus</i>					
	Control	4	6	10	12	14	Control	4	6	10	12	14
	%	%	%	%	%	%	%	%	%	%	%	%
3.6	0	10	30	50	100	100	0	20	35	70	100	100
4.5	0	0	20	70	90	100	0	0	40	75	100	100
6.0	0	25	60	80	90	100	0	0	30	70	100	100
9.0	0	0	10	30	50	60	0	0	10	50	90	100
10.0	0	10	10	30	70	100	0	10	10	25	80	100

(*) With a recovery period of 24 hr.

Effect of pH on the molluscicidal potency of Damsin (Table 3)

Different concentrations of Damsin solution were prepared using standard reference water previously adjusted at pH values of 3.6, 4.5, 6.0, 9.0 and 10.0. Tests using 24 hr exposure and 24 hr recovery periods were made, and the mortality of snails was determined in each test (Gönnert & Struffe, 1962). Results showed that the molluscicidal activity of Damsin was not or only slightly affected by pH values ranging from 3.6 to 10.0.

Effect of sunlight on the molluscicidal activity of Damsin (Table 4)

A stock solution of 500 ppm was made up in distilled water and exposed to direct sunlight for 6 hr. Different dilutions were then prepared. Tests using 6-hr exposure periods and 24-hr recovery periods were made and the mortality percentages of snails were determined.

It is evident from Table 4 that the molluscicidal activity of Damsin is greatly diminished by direct sunlight. At 300 ppm *Biomphalaria alexandrina* showed a mortality of only 40% and *Bulinus truncatus* of 80%. At a 200 ppm concentration of Damsin not exposed to direct sunlight, a 100% mortality was recorded for both snail species.

Effect of river-bed-mud on the molluscicidal potency of Damsin (Table 5)

A number of *B. alexandrina* and *B. truncatus* snails were put into beakers containing solutions of Damsin at different concentrations and river-bed mud. The beakers were shaken continuously for 6 hr in an electric shaker. The results given in Table 5 indicated that 200 ppm of Damsin were required to kill all *B. truncatus* in the presence of 1000 ppm of mud. With *B. alexandrina*, 200 ppm of Damsin gave only a 10% mortality in the presence of a similar concentration of mud.

TABLE 4. Molluscicidal effect of Damsin solutions exposed to direct sunlight for 6 hr.

Concentrations ppm	Mortality after 6 hr. of exposure*	
	<i>Biomphalaria alexandrina</i>	<i>Bulinus truncatus</i>
	%	%
Stock solutions (exposed to sunlight)		
300	40	80
200	10	50
150	0	60
100	0	20
60	0	0
Controls (not exposed to sunlight)		
100**	—	100
200**	100	—

(*) and a recovery period of 24 hr.

(**) minimum concentration for 100% mortality.

TABLE 5. Comparative effects of different concentrations of river-bed mud on the molluscicidal potency of Damsin on *Biomphalaria alexandrina* and *Bulinus truncatus* for 6 hr exposure and 24 hr recovery periods.

Damsin concentration	Mortality of snails in Damsin at the following concentrations of river bed mud (ppm)					
	<i>Biomphalaria</i>			<i>Bulinus</i>		
	5,000	10,000	0 (control)	5,000	10,000	0 (control)
	%	%	%	%	%	%
200	35	10	95.0	100	100	100
150	20	0	72.0	100	65	100
100	20	0	25.0	60	30	100
80	0	0	10.0	20	10	90
60	0	0	0.0	20	0	45
40	0	0	0.0	0	0	15

Effect of temperature and storage on the molluscicidal property of Damsin (Table 6)

Different dilutions of Damsin ranging from 80-500 ppm were prepared and stored for 4 days under the following conditions: one batch was kept at room temperature (27-28°), a second was first boiled for 5 min. and then stored at room

temperature, and a third was kept in the refrigerator at 10°C. At 500 ppm Damsin, a 10% mortality of *B. alexandrina* was attained with the boiled Damsin as compared to a 20% mortality with the refrigerated or normally stored Damsin solutions. In the case of *B. truncatus*, 100% mortality was attained in all cases at the same Damsin concentration.

TABLE 6. Storage stability and molluscicidal potency of Damsin.

Concentration ppm	Mortality after 4 days of storage					
	In refrigerator (10°C)		After boiling		At room temp. (27°C)	
	<i>Biomphalaria</i>	<i>Bulinus</i>	<i>Biomphalaria</i>	<i>Bulinus</i>	<i>Biomphalaria</i>	<i>Bulinus</i>
	%	%	%	%	%	%
Stored solutions						
500	20	100	10	100	20	100
300	0	100	0	100	0	80
200	0	100	0	100	0	30
150	0	60	0	70	0	0
100	0	10	0	10	0	0
80	—	—	0	10	0	0
Controls (freshly prepared)						
100	—	100	—	100	—	100
200*	100	—	100	—	100	—

(*) Minimum concentration causing 100% mortality.

Discussion

The fact that different snail species vary in their susceptibility to different molluscicides necessitated testing the action of the 3 isomeric compounds investigated in this study: Damsin (compound I), Ambrosin (compound II) and Tribromo-Damsin (compound III) on both schistosome vector snails in Egypt, *Biomphalaria alexandrina* and *Bulinus truncatus*. The observed difference in susceptibility of these 2 species to the toxicity of the three compounds is probably due to differences in their enzymatic systems rather than to a different mechanism of action of the compounds. This difference in susceptibility is highly significant with Damsin at a 6-hr exposure period. The increase in mortality with increase of exposure period is normally due to increased absorption of the compound and consequently of increased toxic action.

While the potency of Damsin was found to deteriorate in the presence of mud and sunlight, it was only slightly

affected within a wide range of pH values (3.6-10.0). This might be due to the stability of Damsin within this range of acid and alkaline media, but, in the light of the known general instability of lactones in an alkaline medium, it might be postulated that the hydrolytic product of Damsin in the alkaline range, if present, is also active.

As to the effect of structure variations among the three compounds, it appears that, unlike phenolic compounds, the introduction of bromine atoms to form the Tribromo-Damsin (III) did not effect an increase in the molluscicidal activity of Damsin. Moreover, the hydrogenation of the cyclopentanone ring of Ambrosin (II) to form Damsin (I) did not effect changes in the molluscicidal activity.

In conclusion, although molluscicidal activity of the principal biologically active constituents of *Ambrosia maritima* is promising, the isolation of these constituents is expensive. However, a suitable plant extract may be of value for field application.

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THE MOLLUSCICIDAL PROPERTIES OF SOME BAYLUSCIDE HOMOLOGUES

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The aim of controlling schistosomiasis by the eradication of snails has encouraged the search for effective molluscicides (Shoeb, 1975). Investigations in this field produced Bayluscide (Gönnert & Schraufstaetter, 1959) as the present molluscicide of choice. The compound is effective at 1 ppm (Jeney & Zsolnai, 1967; Duhm et al., 1961). As Bayluscide has the disadvantage of being affected by strong irradiation from the sun (Pawar & Thisumalachar, 1965), by acidic pH (Fox et al., 1963) and is toxic to fishes (Kozianowski, 1964), further work in this area of research is still needed. The present investigation deals with 2 Bayluscide homologues selected from a series of nitro-salicylanilides that have been prepared and tested in our laboratory. The molluscicidal properties of the compounds were studied in the pure state and also in their mixture, as it was obtained on nitration, before separation, for reasons of economy. These homologues are (Fig. 1) :

- I. 5-nitro-2',4'-dichloro salicylanilide.
- II. 3-nitro-2',4'-dichloro salicylanilide.
- III. a mixture of I and II in the proportion of 5.5 : 1.

Material and Methods

The two known snail intermediate hosts of schistosomiasis in Egypt *Bulinus truncatus* and *Biomphalaria alexandrina* were used in the present study. The snails

were collected from irrigation canals located in Giza Governorate that had not been treated with molluscicides. The snails were adapted to laboratory conditions for a period of at least 3 months before being used in the toxicity tests.

The 5-nitro- (I) and the 3-nitro- (II) salicylanilides were synthesized from the corresponding nitrosalicylic acids. Compound III, which is a mixture of I and II in the ratio of 5.5 : 1, was synthetically obtained from a mixture of the parent nitroacids as obtained by nitration of salicylic acid.

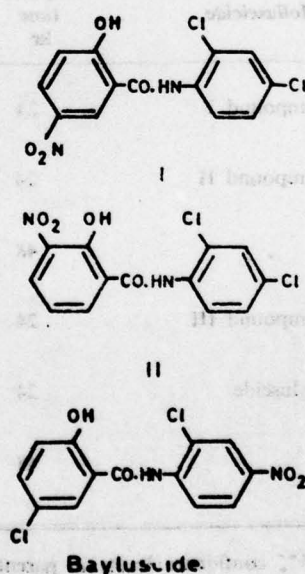


Fig. 1. Structural formulas of Bayluscide and its two homologues.

Stock solutions of 100 ppm were freshly prepared on the basis of weight/volume in distilled water. Series of concentrations that permit the computation of LC_{50} values were prepared. Standard test procedures (WHO, 1953, 1965) were followed throughout this study. The effect of the three molluscicides, as compared with Bayluscide, has been expressed in terms of LC_{50} and LC_{90} (Litchfield & Wilcoxon, 1949).

Results

Comparative susceptibility of *Biomphalaria alexandrina* and *Bulinus truncatus* to the molluscicidal action of compounds I-III

It is evident from Table 1 and from the figures that the difference in susceptibility of both snail species towards compound I (Fig. 3) and Bayluscide (Fig. 2) is only slight. However, for compounds II and III (Fig. 4 and 5) this difference is more detectable. Whereas the LC_{90} of compound II against *Biomphalaria* dropped from 0.88 ppm after a 24 hr exposure to 0.47 ppm after a 48 hr exposure, the corresponding figure for Bayluscide was not changed by increasing exposure time (Fig. 6). Similarly, the LC_{90} of compound II against *Bulinus* fell from 0.53 ppm after an exposure of 24 hr to 0.26 ppm after exposure for 48 hr, whereas, for Bayluscide, the corresponding LC_{90} of 0.255 ppm after 24 hr was not changed by increasing exposure time to 48 hr (Fig. 6).

TABLE 1. Comparative susceptibility of the 2 intermediate snails hosts to different molluscicides.

Molluscicide	Exposure time hr	<i>Biomphalaria</i>		<i>Bulinus</i>	
		LC_{50} *ppm	LC_{90} ppm	LC_{50} *ppm	LC_{90} ppm
Compound I	24	0.34 (0.28-0.40)	0.52	0.27 (0.21-0.34)	0.44
Compound II	24	0.64 (0.55-0.74)	0.88	0.31 (0.24-0.39)	0.53
	48	0.32 (0.26-0.39)	0.47	0.165 (0.13-0.21)	0.265
Compound III	24	0.44 (0.33-0.58)	0.85	0.32 (0.244-0.419)	0.58
Bayluscide	24	0.088 (0.068-0.108)	0.32	0.087 (0.067-0.107)	0.255
	48	0.255 (0.210-0.303)	0.31	0.145 (0.115-0.183)	0.21

(*) 95% confidence limits in parentheses.

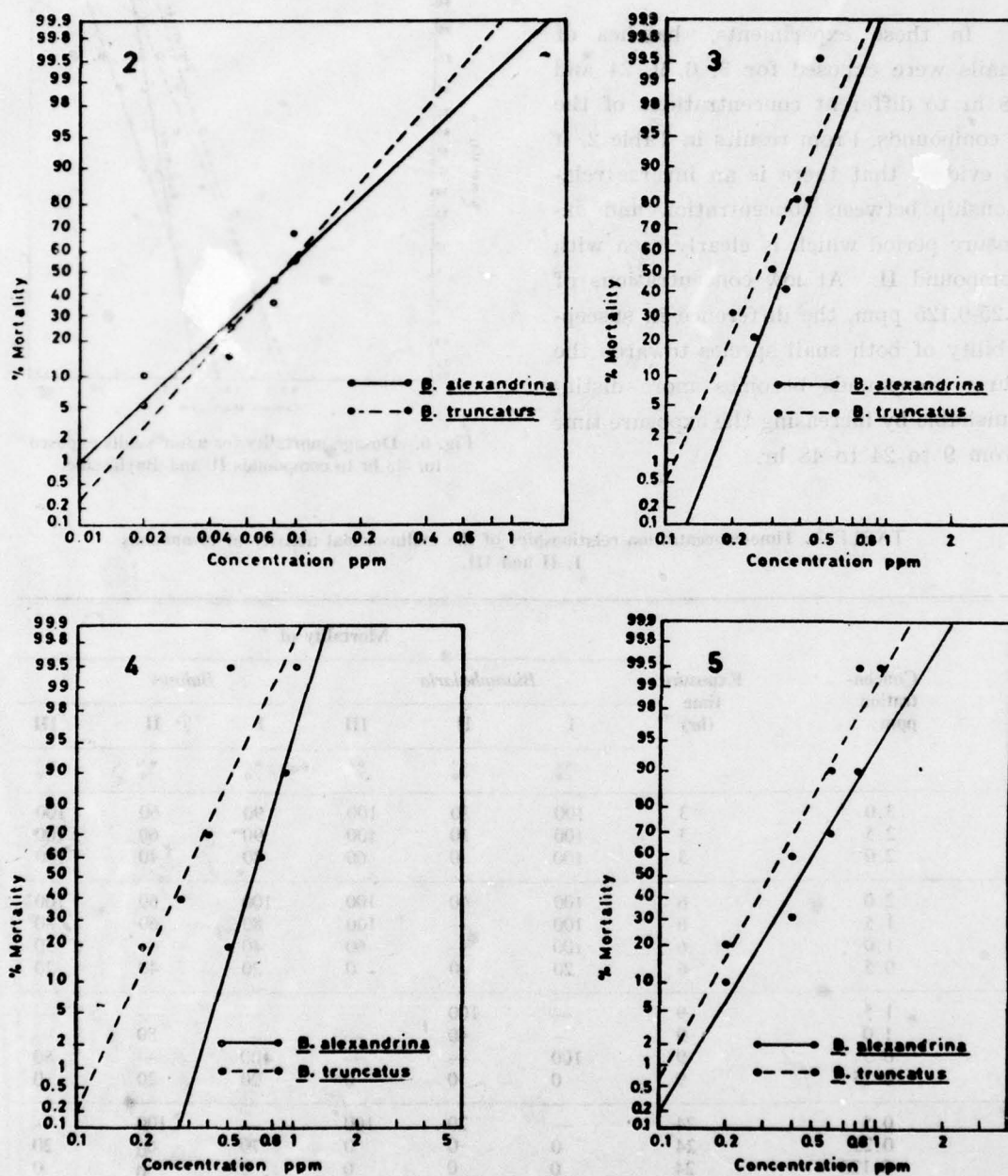


Fig. 2-5 — Dosage mortality for adult snails exposed for 24 hr to: 2. Bayluscide; 3. Compound I; 4. Compound II; 5. Compound III.

Time-concentration relationships of the molluscicidal activity of compounds I-III

In these experiments, batches of snails were exposed for 3, 6, 9, 24 and 48 hr to different concentrations of the 3 compounds. From results in Table 2, it is evident that there is an inverse relationship between concentration and exposure period which is clearly seen with compound II. At low concentrations of 0.25-0.125 ppm, the difference in susceptibility of both snail species towards the three compounds becomes more distinguishable by increasing the exposure time from 9 to 24 to 48 hr.

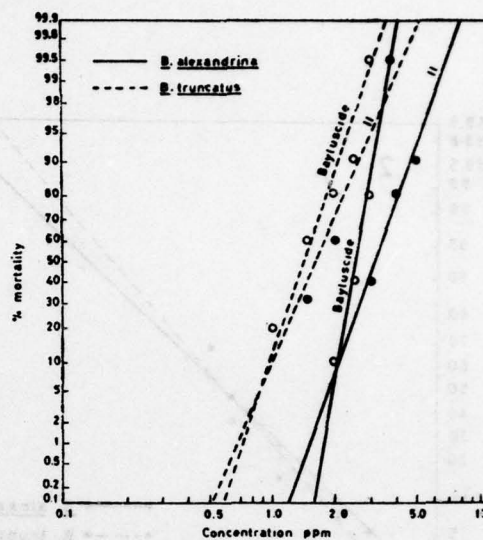


Fig. 6. Dosage mortality for adult snails exposed for 48 hr to compounds II and Bayluscide.

TABLE 2. Time-concentration relationships of the molluscicidal activity of compounds I, II and III.

Concentration ppm	Exposure time (hr)	Mortality of					
		<i>Biomphalaria</i>			<i>Bulinus</i>		
		I	II	III	I	II	III
		%	%	%	%	%	%
3.0	3	100	20	100	90	60	100
2.5	3	100	10	100	90	60	100
2.0	3	100	0	60	80	40	100
2.0	6	100	60	100	100	60	100
1.5	6	100	—	100	80	60	80
1.0	6	100	—	60	40	—	50
0.5	6	20	0	0	20	40	20
1.5	9	—	100	—	—	—	—
1.0	9	—	40	—	—	80	—
0.5	9	100	—	—	100	—	80
0.25	9	0	0	0	20	20	0
0.5	24	—	20	100	—	100	—
0.25	24	0	0	0	70	60	20
0.125	24	0	0	0	0	0	0
0.25	48	0	100	40	—	—	—
0.125	48	0	10	0	40	100	70
0.05	48	0	0	0	0	0	0
Control	48	0	0	0	0	0	0

TABLE 3. Effect of pH on the molluscicidal potency of compounds I, II and III.

Concentration ppm	Mortality of snails exposed for 24 hr* to the following pH values							
	<i>Biomphalaria alexandrina</i>				<i>Bulinus truncatus</i>			
	4.5 %	6 %	9 %	10 %	4.5 %	6 %	9 %	10 %
Compound I								
0.125	40	0	0	0	100	0	0	0
0.25	100	100	0	0	100	80	0	0
0.5	100	100	60	40	100	100	20	80
1.0	100	100	80	80	100	100	80	80
1.5	100	100	100	80	100	100	100	80
Control	0	0	0	0	0	0	0	0
Compound II								
0.125	0	0	0	0	80	0	0	0
0.25	90	0	0	0	100	40	40	0
0.5	100	80	20	0	100	100	80	40
1.0	100	100	80	0	100	100	100	80
1.5	100	100	100	80	100	100	100	80
Control	0	0	0	0	0	0	0	0
Compound III								
0.125	0	0	0	0	40	0	0	0
0.25	40	60	0	0	60	80	20	40
0.5	80	80	60	0	80	60	60	30
1.0	100	100	60	20	100	100	80	40
1.5	100	100	100	100	100	100	100	100
Control	0	0	0	0	0	0	0	0

(*) Recovery period of 24 hr.

Effect of pH on the molluscicidal potency of compounds I-III

For studying the effect of pH values on the molluscicidal potency of compounds I-III, different concentrations were prepared using standard reference water previously adjusted at pH values of 4.5, 6, 9 and 10. Tests using 24 hr exposure and 24 hr recovery periods were made, and the mortality of snails was determined in each test (Gönnert & Struffe, 1962). Results given in Table 3 indicate that the susceptibility of *B. truncatus* towards the three compounds in-

creases by increasing the acidity of the molluscicide solution. The activity of the three compounds progressively increased when increasing the acidity to pH 4.5, but decreased by increasing the alkalinity to pH 10.

Effect of sunlight on the molluscicidal activity of compounds I-III

A stock solution of 10 ppm was made up in distilled water and exposed to direct sunlight for 6 hr, then different dilutions were made. Tests using 24-hr exposure periods and 24-hr recovery periods were

TABLE 4. Effect of sunlight* on the molluscicidal activity of compounds, I, II and III.

Concentration** ppm	Mortality of					
	<i>Biomphalaria</i>			<i>Bulinus</i>		
	I	II	III	I	II	III
	%	%	%	%	%	%
0.125	0	0	0	0	0	0
0.25	0	0	0	60	40	10
0.5	100	40	100	90	70	60
1.0	100	80	100	100	90	80
1.5	100	100	100	100	80	100
2.0	100	100	100	100	100	100
Control***	100	100	100	100	100	100
	(0.5)	(1)	(1)	(0.5)	(0.5)	(0.8)

(*) Stock solutions were exposed to direct sunlight for 6 hr.

(**) Exposure and recovery periods were 24 hr.

(***) No exposure to direct sunlight; values in parentheses indicate the lowest concentration of molluscicide, in ppm, to produce 100% mortality.

made and the mortality percentage of snails was determined. From results in Table 4, it is obvious that the three compounds are resistant to the effect of the sun's radiation, specially at concentrations above 1 ppm.

Effect of river bed mud on the molluscicidal activity of compounds I-III

Under natural conditions flowing water has sufficient turbulence to cause rapid mixing of particles in the water. In an attempt to simulate this condition in the laboratory, solutions of compounds I-III were prepared with water containing different suspensions of river bed mud. A number of *B. alexandrina* and *B. truncatus* snails were placed into beakers containing these different concentrations of mud and compounds I-III, and the beakers were shaken continuously on an electric shaker for 6 hr. From Table 5 it is evident that whereas compound I is stable at the different mud concentrations, compounds II and III are less stable, specially at low concentrations.

Effect of storage at 2 temperatures on the molluscicidal activity of compounds I-III

Different dilutions of compounds I-III were either stored at room temperature (27-28°C) or kept in the refrigerator at 10°C for 7 days. The activity of the stored solutions was tested on the snails used through 24-hr exposure and 24-hr recovery periods. From Table 6 it is clear that the molluscicidal activity of compounds I-III is not affected by storage at concentrations above 1 ppm.

Effect of a temperature of 8°C on the molluscicidal activity of compounds I-III

The tested snails were exposed to different dilutions of compounds I-III at 8°C for 24-hr exposure periods followed by a similar recovery period. The data indicate (Table 7) that the activity of the three compounds is not affected by a relatively low temperature of 8°C at concentrations from 1 ppm upwards. At lower concentrations activity is slightly affected.

TABLE 5. Comparative effects of different concentrations of river bed mud on the molluscicidal potency of compounds I, II and III on *Biomphalaria alexandrina* and *Bulinus truncatus* for 6 hr exposure and 24 hr recovery periods.

Molluscicide concentration ppm	Mortality of snails exposed to compounds I, II, and III with different concentrations of river bed mud (ppm)								
	I			II			III		
	5000	10000	0	5000	10000	0	5000	10000	0
	(Control)			(Control)			(Control)		
	%	%	%	%	%	%	%	%	%
<i>Biomphalaria alexandrina</i>									
0.5	80	60	100	0	0	40	20	40	80
1.0	100	100	100	60	20	100	80	80	100
1.5	100	100	100	40	60	100	100	100	100
2.0	100	100	100	40	80	100	100	100	100
2.5	100	100	100	80	80	100	100	100	100
3.0	100	100	100	100	100	100	100	100	100
<i>Bulinus truncatus</i>									
0.5	100	100	100	100	100	100	100	100	100
1.0	100	100	100	100	100	100	100	100	100

TABLE 6. Effect of storage on the molluscicidal potency of compounds I, II and III at different temperatures after 7 days.

Concentration ppm	Mortality of					
	<i>Biomphalaria</i>			<i>Bulinus</i>		
	I %	II %	III %	I %	II %	III %
A. At refrigerator temperature (10°C)						
0.125	0	0	0	0	0	0
0.25	0	0	0	0	40	40
0.5	80	50	60	80	70	60
1.0	100	100	100	90	80	90
1.5	100	100	100	100	100	100
2.0	100	100	100	100	100	100
Control*	100	100	100	100	100	100
	(0.5)	(1.0)	(1.0)	(0.5)	(0.5)	(0.8)
B. At room temperature (27°C)						
0.125	0	0	0	0	0	0
0.25	20	0	30	30	40	20
0.5	100	30	70	100	100	60
1.0	100	100	100	100	100	100
1.5	100	100	100	100	100	100
Control*	100	100	100	100	100	100
	(0.5)	(1.0)	(1.0)	(0.5)	(0.5)	(0.8)

(*) Values in parentheses indicate the lowest concentration of molluscicides, in ppm, producing 100 % mortality.

TABLE 7. Effect of 24 hr exposure to 8°C on the molluscicidal activity of compounds, I, II and III.

Concentration ppm	Mortality of					
	<i>Biomphalaria</i>			<i>Bulinus</i>		
	I	II	III	I	II	III
	%	%	%	%	%	%
0.125	0	0	0	0	0	0
0.25	0	0	0	20	40	20
0.5	80	20	20	20	60	20
1.0	100	10	80	100	100	80
1.5	100	40	100	100	100	80
2.0	100	80	100	100	100	100
2.5	100	100	100	100	100	100
Control	0	0	0	0	0	0

Discussion

In continuation of a programme of research aimed at the finding of efficient molluscicides, the three molluscicides under investigation (I, II and III) have been selected from a large number of nitrosalicylanilides that were newly synthesized in our laboratory and tested for molluscicidal activity.

As regards compound I, a 100% mortality of both snail species was attained within 9 hr at 0.5 ppm (Table 2), a rate that could not be attained at lower concentrations by increasing the exposure time. This behaviour indicates that :

- Compound I is a quick acting molluscicide ;
- Its maximum activity depends mainly on its concentration ;
- After more than 9 hr, the time factor is of no further value for its activity.

On the other hand, the characteristic features pertaining to compound II are the following :

- It is a slow acting molluscicide, i.e., its action reaches a peak after a 48 hr

exposure period at a minimum dose of 0.25 ppm for *B. alexandrina* and 0.125 ppm for *B. truncatus* (Table 2). This indicates that its activity depends mainly on the time factor ;

- It showed distinct specificity towards *B. truncatus*.

Compound III, which is a mixture of I and II in the proportion of 5.5 : 1, which is obtained in that proportion during preparation and was not purified for economic reasons, has characteristic common features ; its maximum activity is dependent to a large extent on the time factor.

From the structural point of view, it is assumed that the exchange of the 5-chlorine atom in Bayluscide and its 4'-nitro (4-NO₂) group forms compound I, and that substituting the 5-chlorine atom of Bayluscide by a 3-nitro group and its 4'-nitro group by a 4-chlorine atom gives compound II. Both nitro-salicylanilides I and II are comparable to Bayluscide in activity but have the advantages of being resistant to an acidic pH, and to sunlight ; they also may prove to be more economic.

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**EFFECT OF CERTAIN INSECTICIDES ON THE FRESH WATER
SNAILS *BIOMPHALARIA ALEXANDRINA* AND *BULINUS TRUNCATUS***

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ABSTRACT

The molluscicidal and ovicidal activity of 19 different compounds commonly used as insecticides were tested against the egg-masses, newly hatched and adults of the fresh water snails *Biomphalaria alexandrina* and *Bulinus truncatus*. The compounds tested were the carbamate Zectran; two chlorinated hydrocarbons, Lindane and DDT/Lindane; Karathane, from among the dinitrophenyl compounds, and 15 organophosphorous compounds. Bayluscide was used as a reference compound.

The LC_{50} and LC_{90} values for adult snails were lower for *Bulinus truncatus* than for *Biomphalaria alexandrina*. Newly hatched *B. alexandrina* were more susceptible to the tested compounds than adult snails. However, they were more resistant to Bayluscide than were adults. Egg-masses exhibited a higher resistance to most experimental insecticides than adult snails from both species.

CONTROL OF *SCHISTOSOMA MANSONI* TRANSMISSION IN AN ISOLATED VALLEY IN ST. LUCIA, WEST INDIES

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ABSTRACT

A programme to control *Biomphalaria glabrata* in an isolated valley in St. Lucia began in September 1970. Although a molluscicide (Bayluscide e.c. 25% a.i.) was the only effective control agent, other methods were tried.

The predominant snail habitat is a series of banana drains, their total length being 1200 km; 800 km of these were infected with snails, prior to control. The drains flow into collector drains which eventually discharge into the main valley river.

Eleven hectares of marshes are mainly on the valley floor at the junction with the valley sides, although some small ones exist near the top of the valley walls.

An attempt to drain marshy areas proved unsatisfactory in the majority of cases, but the protection of a spring and pool and the subsequent draining of a lower stretch of marsh was successful. The planting of certain trees in a marshy area in order to dry it up was also unsuccessful. Aerial spraying of a 12 ha marsh with molluscicide was partially successful.

Reduction of *B. glabrata* populations by molluscicide was successful, and resulted in a decline in *Schistosoma mansoni* transmission. This was achieved over 4.5 years by molluscicide application to various habitats in the valley.

A strategy was designed to control the number of snails in all habitats, but particularly in the flowing ones, where transmission of *S. man-*

soni was found to be seasonal, but much more important than in static habitats.

An initial intensive treatment was given to all habitats in September/October 1970 and this was followed by a surveillance-treatment programme where eventually the surveillance cycle was reduced to two weeks. Two further intensive treatments in small localised areas were given in November 1971 and July 1974, but by this time the area producing live snails had been drastically reduced from its original size.

The banana drains and marshes were hand sprayed and the flowing habitats were treated by applying the molluscicide for 6 hr from a constant-flow dispenser.

Assessment was by parasitological investigations of the human population, the monitoring of specific index sites and the detection of cercariae in wild-caught snails.

Incidence amongst 0-10 year old children living in settlements close to the river fell from 22% in the last year before control to 4.3% between 1974 and 1975. In the same age group prevalence fell from 34.9% to 8.1% and the geometric mean of egg output of infected children decreased from 29 to 15 eggs per ml of faeces.

In April 1975 all the infected people were treated and the above-mentioned programme was discontinued. It was replaced by a simplified scheme based on surveillance of flowing water habitats.

CONTROL OF URINARY SCHISTOSOMIASIS IN SOUTHWESTERN IRAN

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ABSTRACT

Khuzestan, the endemic bilharziasis area in Iran, is already under an extensive development programme which includes the construction of several dams and the extension of new irrigation systems on a large scale.

The control of urinary schistosomiasis by a combination of chemotherapy, sanitation and mollusciciding has been underway since 1966. Although the results obtained so far in the control of bilharziasis in Khuzestan are very encouraging, the danger of reinfestation of the area and the spread of bilharziasis due to the extension of irrigation networks should not be overlooked. The extension of irrigation networks has already been completed for 167,000 hectares of land around Dezful, and much more land in other parts of Khuzestan will be irrigated in the future. In spite of very close supervision by the Bilharziasis Project in the irrigation area, particularly in the sugar cane area south of Dezful, a high propor-

tion of canals have gradually become infested with *Bulinus truncatus*.

However, in spite of the presence of this intermediate host in the area, the spread of bilharziasis has been prevented by the regular examination of all inhabitants and treatment of all new cases. Since 1966, 15,000 patients have been treated and at present the percentage of infected persons is less than 4-5%. Every year several hundred patients are discovered by case finding and treated immediately. Considering the cases not detected during urine examination, patients not treated during the operation and patients who remained positive after treatment, it is estimated that each year the number of infected persons in each village had been reduced by 80%.

The general results are encouraging and show the possibility of schistosomiasis control in Iran.

**STUDIES ON POPULATION DENSITY AND INFECTION RATE OF
ONCOMELANIA HUPENSIS LINDOENSIS, THE SNAIL
INTERMEDIATE HOST OF *SCHISTOSOMA JAPONICUM* IN
LINDU VALLEY, CENTRAL SULAWESI, INDONESIA**

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In 1971, after the discovery of *Oncomelania hupensis lindoensis*, the elusive snail intermediate host of *Schistosoma japonicum* in Lindu Valley, Central Sulawesi (Carney et al., 1973a), our primary concern was to study the population dynamics and ecology of the snail. However, quantitative sampling of the molluscan population proved to be a difficult task. The tiny amphibious snail, no larger than a grain of rice, was not easy to find, especially when the vegetation in the habitat is very dense. Moreover, the chestnut brown color of the shell blends well with the micro-habitat. But the greatest problem resided in the diverse habitats of the snail, so that one method of sampling, which was useful and appropriate in a given situation, proved inapplicable to others. Thus, in fallow or abandoned rice fields, it was possible to use any method of exhaustive count, whereas, in forest ecotonal zones and low-lying swampy areas where water is present and the mud is several feet deep, sampling of any kind became nearly impossible. It was therefore decided to try several methods of snail sampling and later on to adopt one single technique for use in our control programme.

The present study, which progressed for one year, is part of a pilot scheme designed to control and prevent the possible spread of the disease from Lindu Valley into the adjoining Palu and Palolo valleys where more than 70,000 inhabitants would be at risk to infection.

Description of the Study Area

The endemic area of Lindu is situated in the Tokalekaju mountain range at an elevation of 950 m in Central Sulawesi (Celebes), Indonesia. This remote mountain valley with its 1,500 inhabitants is accessible only by foot from the nearest road and is about 70 km south-east of the provincial capital, Palu.

Over 70 snail colonies or foci have been found in the lowlands around Lake Lindu; but the lake itself, which is 10 km long and 6 km wide, is free from *Oncomelania* snails. The Gumbasa river, which is the only outlet from the lake into the adjoining Palu valley has also been surveyed. The area was found negative for the molluscan host and for infected wild mammals. Although the snails are widely distributed in the 50 km² area of Lindu Valley, their distribution was observed to

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be focal or localized, as described by Carney et al. (1973b).

In general, habitats of *Oncomelania* fall into two categories, namely: the natural foci and the disturbed habitat (Sudomo & Carney, 1974). The snail colonies in the virgin forest belong to the first group whereas foci, found in fallow or abandoned rice fields, fall into the second category. Rice fields which are in constant cultivation do not support growth and development of the snail but uncultivated grassy areas with rich silt soil adjacent to the rice paddies favor habitation by the species. Likewise, dense vegetation along the banks of the existing crude irrigation network in the Paku farming area support *Oncomelania* snails. Natural foci were found in a variety of undisturbed areas, chiefly in ecotonal zones between the forest and the lowlands. These habitats were spring-fed areas with a silty substrate that remain moist and wet throughout the whole year and are well shaded by medium and high tropical vegetation. The snails were observed crawling over the silty soil or attached to tanned leaves or any other flotsam available. Some of the foci were located in small pockets where forest vegetation bordered the lake shore. These spring-fed areas have a typically sandy substrate with medium size stones scattered about. *Oncomelanids* were found on the rocks, on the undersurface of tanned leaves, dead branches and other flotsam, obviously browsing for food.

Materials and Methods

Three methods were used for determining snail population density, namely:

(1) Man-per-minute method. The snail habitat is divided into stations, the distance between two stations being about 5 m. The snails were collected in each

station for 5 min. within an area of about 1 m². The snail catch was put into coded cloth bags and brought to the laboratory for counting, measuring, sex determination and examination for parasitic infection. Snail population density was calculated by dividing the number of snails collected by total sampling time. The result is expressed in number of snails collected per man per minute.

(2) Ring sample. At each station an iron ring, with a diameter of 13.5 cm similar to that used by Pesigan et al. (1958), is dropped on the soil and all the snails inside are collected with a pair of forceps and placed in cloth bags which are identified by an appropriate numbering system. The contents of the bags are then investigated in the laboratory as above. The snail population density, expressed in number of snails per square meter, is obtained by dividing the total number of snails collected by the number of samples taken, times 70.

(3) Core sample. In this method, a piece of brass tube with a diameter of 13.5 cm is pushed into the mud and the plug thus obtained is washed through a series of sieves with mesh-sizes ranging from 12.7 mm to 1 mm. The snails collected from the screens are transferred into coded cloth bags and brought to the laboratory for sorting and examination. The population density is calculated by dividing the number of snails collected by the number of samples, times 70. As in the «ring» method described above, results are then expressed in number of snails per square meter.

Results

Results of the quantitative snail counts by the 3 methods of snail sampling which were tried out for a period of 1 year in the Luo focus in Lindu

Valley, in order to determine seasonal variations in population density and infection rates, indicate (Table 1) that the highest collections were those obtained with the exhaustive core sampler or plug method. Figures for the «ring» method

were approximately 1/4 to 1/5 of those taken by the plug technique. The man-per-minute method gave rather low figures. It gives only an indication of the relative abundance of the snails during each period of collection.

TABLE 1. Comparative studies among 3 methods of sampling *Oncomelania hupensis lindoensis* snails in Luo focus, Lindu Valley, Central Sulawesi, Indonesia⁺

Sampling	Man./min. method*	Ring method**	Core sample (plug)method***
23—8—73	3.19	980.	—
23—9—73	3.00	109.2	—
23—10—73	3.58	—	1253
27—11—73	3.20	397.6	2135
23—12—73	3.90	441.7	1309
24—1—74	3.01	288.4	1141
24—2—74	2.43	179.2	1337
23—3—74	1.13	95.9	1071
24—4—74	2.13	352.6	1071
23—5—74	0.93	41.3	637
23—6—74	1.35	114.1	735
23—7—74	1.12	93.1	686

+ From Carney and Sudomo (1974) unpublished data. (*) Mean of 30 samples.

(**) Mean of 10 samples

(***) Mean of 10 samples.

The snail infection rates in 3 separate habitats where the «ring» method of collection was employed are given in Tables 2, 3 and 4. Schistosome infection was

determined by crushing of the specimens and examination under a dissecting microscope for the presence of schistosome cercariae.

TABLE 2. Results of monthly collection of *Oncomelania hupensis lindoensis* in Anca focus No. 2 using the «ring» method and numbers found infested with *Schistosoma japonicum**.

Month of collection	No. of snails collected in 50 samples	Approx. density per m ²	Nos. positive	Infection rate %
Sept. 1974	173	242.2	2	1.15
Oct. 1974	184	257.6	3	1.63
Nov. 1974	59	82.6	0	0
Dec. 1974	157	219.8	2	1.27
Jan. 1975	95	133	0	0
Feb. 1975	157	219.8	3	1.91
Mar. 1975	111	155.4	0	0
Apr. 1975	56	78.4	0	0
May 1975	88	123.2	1	1.13
June 1975	49	68.6	0	0
July 1975	77	107.8	1	1.29
Aug. 1975	102	142.8	0	0
Sept. 1975	107	149.8	0	0

(*) Infection determined by crushing and examination under a dissecting microscope.

TABLE 3. Results of monthly collection of *Oncomelania hupensis lindoensis* in Paku focus No. 5 using the "ring" method and numbers found infested with *Schistosoma japonicum**

Month of collection	No. of snail collected in 20 samples	Approx. density per m ²	Nos. positive	Infection rate %
Sept. 1974	60	210	0	0
Oct. 1974	27	94.5	1	3.70
Nov. 1974	49	171.5	0	0
Dec. 1974	18	63	1	5.55
Jan. 1975	5	17.5	0	0
Feb. 1975	37	129.5	1	2.7
Mar. 1975	17	59.5	3	17.65
Apr. 1975	4	14	0	0
May 1975	10	35	0	0
June 1975	11	38.5	0	0
July 1975	38	133	0	0
Aug. 1975	38	133	0	0
Sept. 1975	22	77	0	0

(*) Infection determined by crushing and examination under dissecting microscope.

TABLE 4. Results of monthly collection of *Oncomelania hupensis lindoensis* in Lombu focus using the "ring" method and numbers found infested with *Schistosoma japonicum**

Month of collection	No. of snails collected in 240 samples	Approx. density per m ²	Found positive	Infection rate %
Sept. 1974	187	54.54	2	1.07
Oct. 1974	281	81.95	2	0.71
Nov. 1974	140	40.83	8	5.71
Dec. 1974	175	51.04	3	1.71
Jan. 1975	101	29.46	0	0
Feb. 1975	161	46.96	5	3.11
Mar. 1975	76	22.17	1	1.31
Apr. 1975	111	32.2	1	0.9
May 1975	53	15.4	0	0
June 1975	72	21	0	0
July 1975	126	36.75	3	2.38
Aug. 1975	195	56.87	4	2.05
Sept. 1975	189	55.12	11	5.82

(*) Infection determined by crushing and examination under a dissecting microscope.

Figures 1 and 2 show snail densities and infection rates in three separate habitats in Lindu valley. It will be seen that the population densities are erratic. There seems to be no definite season or

pattern for infection rates. This is presumably due to the fact that rain is continuous in the valley throughout the year (Table 5).

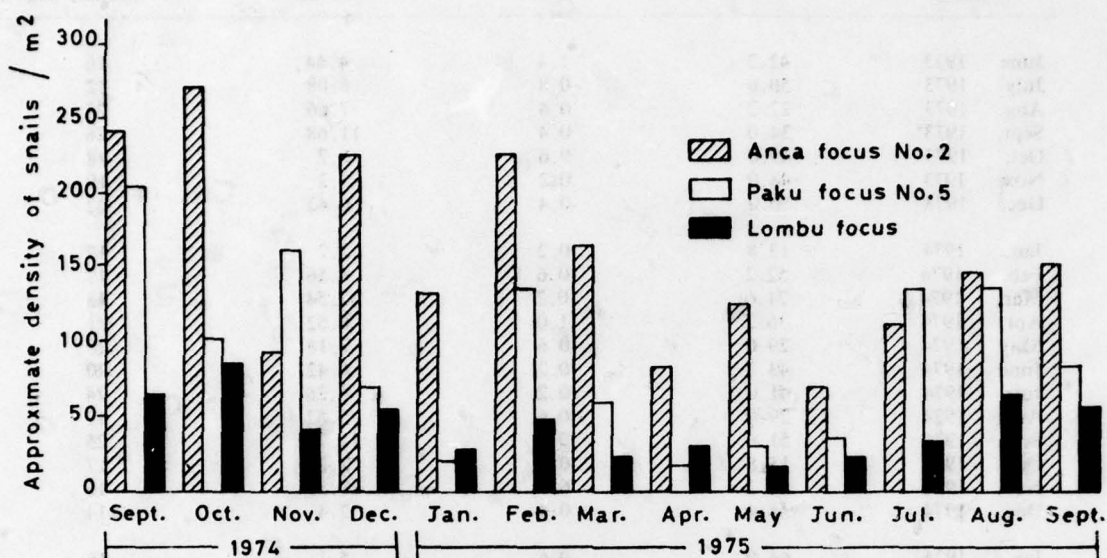


Fig. 1. Population densities of *Oncomelania hupensis lindoensis* in 3 habitats in Lindu Valley, Central Sulawesi, Indonesia (1974-1975).

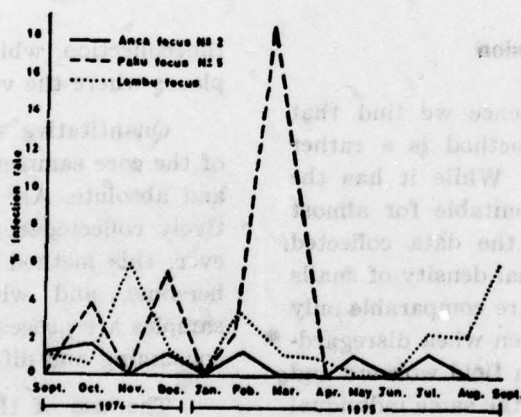


Fig. 2. Infection rates of *Oncomelania hupensis lindoensis* in 3 habitats in Lindu Valley, Central Sulawesi, Indonesia.

TABLE 5. Rainfall in mm in Lindu Valley (1973-1975)

Month	Max.	Min.	Mean	No. of rainy days *
June 1973	42.2	1.4	4.44	16
July 1973	50.6	0.8	6.98	12
Aug. 1973	27.2	0.4	7.66	28
Sept. 1973	34.0	0.4	11.68	26
Oct. 1973	49.0	0.6	6.7	18
Nov. 1973	48.0	0.2	5.2	19
Dec. 1973	50.0	0.4	6.42	22
Jan. 1974	13.8	0.2	2.2	17
Feb. 1974	52.2	0.6	4.56	17
Mar. 1974	21.6	0.2	2.54	13
Apr. 1974	36.2	1.0	6.52	21
May 1974	29.0	0.6	7.18	28
June 1974	43.2	0.2	6.42	20
July 1974	41.0	0.2	6.26	24
Aug. 1974	29.0	0.6	5.52	17
Sept. 1974	51.6	0.4	11.72	25
Oct. 1974	13.8	0.2	2.2	17
Nov. 1974	66.2	6.0	21.35	16
Dec. 1974	34.4	0.4	2.4	14
Jan. 1975	64.0	0.6	5.1	16
Feb. 1975	35.0	0.6	25.66	18
Mar. 1975	31.6	0.4	4.92	19
Apr. 1975	62.4	0.8	9.86	18
May 1975	62.6	0.6	9.72	20
June 1975	56.0	0.4	7.86	20

(*) Not less than 0.254 mm.

Discussion

From our experience we find that the man-per-minute method is a rather subjective technique. While it has the advantage of being suitable for almost all kinds of habitat, the data collected do not reflect the actual density of snails in the focus. Results are comparable only in a relative sense, even when disregarding variations between field workers and in the performance of the same individual collector. In this method, collection would depend on the care and efficiency of the collector. Moreover, where snail density is high and vegetation is thick, it is likely that the density recording will become low due to the difficulties encountered in

the collection, while it will be higher in places where the vegetation is less dense.

Quantitative sampling with the use of the core sampler or the plug is precise and absolute. All the snails are exhaustively collected regardless of size. However, this method is laborious and cumbersome, and when large numbers of samples are processed it can be too time-consuming and difficult.

The use of the ring sample has a number of advantages. It is quick and accurate enough to give an indication of the density of snails in a given area. Since the objective of our control programme is to get an approximate population density before and after implementation of

the control measures, the results in this type of sampling seem reasonable enough. The disadvantages are that smaller specimens are missed as a result of under-collection and that in places which are under water or have a dense growth of vegetation sampling becomes difficult. In our control programme it is anticipated that the snail habitats in Paku area will progressively become dry and manageable as a result of agro-engineering measures or modification of the environment. Because of this, it is felt that the sampling for the snails using the «ring» method would be satisfactory for evaluation purposes.

Because snails flourish and schistosomiasis is transmitted throughout the year, the time of Control activities in an overall Control Programme can be initiated at any time of the year.

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LABORATORY OBSERVATIONS ON THE EFFECT OF AESTIVATION ON OVIPOSITION IN *BULINUS (PHYSOPSIS) NASUTUS*

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Bulinus (Physopsis) nasutus is the principal molluscan host of *Schistosoma haematobium* in Sukumaland, Tanzania. The species, which seems to be limited to Eastern Africa, is known for its preference for temporary habitats and also for its remarkable response to desiccation (Webbe, 1962; McCullough et al. 1968; Matovu, 1974). Webbe (1962) in his 2-year study of the biology of *B. (P.) nasutus* observed that the species is even capable of harbouring an infection for a period of up to 98 days in aestivation. This author noted, as did Shiff (1964), that rainfall seems to stimulate breeding activities in *B. (P.) nasutus* and *B. (P.) globosus* respectively. McCullough et al. (1968) in their studies at Misungwi, Tanzania, suggested that *B. (P.) nasutus* seems to be evolving towards an amphibious mode of life.

In the present studies the effect of aestivation on oviposition rates was studied in the laboratory for 4 weeks.

Materials and Methods

1. Material

The animals used in the studies were collected from natural habitats except for one population of aestivating snails which was collected from an artificial pond very similar to a natural pond. Prior to the studies in the laboratory all habitats had been under observation for at least 4 weeks. Only snails of more or less com-

parable size or age were used for each particular experiment. A total of 6 batches, of which 3 had been aestivating, were used. Their numbers and average sizes are shown in Table 1.

2. Methods

Aestivating snails were collected by scraping the surface of dried up ponds with a spoon. A scoop was employed in collecting non-aestivating animals.

In the laboratory the snails were first put in beakers containing filtered lake water to re-activate aestivating snails and also to screen all snails for cercariae. The animals were then transferred to enamel trays in groups of 20 (first and second experiments) and 15 (third experiment).

The snails were fed on boiled and dried lettuce. The trays were checked daily in the morning for egg masses. Dead snails, unfinished lettuce and faeces were removed daily. The water in the trays was changed after 2 weeks.

For the purpose of comparing the sizes of the egg masses and also the number of embryos per mass, polythene sheets of 3-4 sq.cm were put in the trays, and on these numerous egg-masses were deposited. The sheets could then be removed, the egg-masses measured and the embryos counted under a dissecting microscope.

TABLE 1. Total number of *Bulinus* (*P.*) *nasutus* snails used and their average sizes.

Experiment		No. of snails used	Average size of 40 snails (mm)
I	after aestivation	80	11.5
	active controls	80	12.2
II	after aestivation	80	8.5
	active controls	80	8.8
III	after aestivation	60	13.9
	active controls	60	14.3

Results

1. Re-activation period and infections

In all three aestivating populations the snails needed 45 min. to 1 hr to become active again. Screening all six populations under a table lamp (60W) for 45 min. revealed no trematode infection.

2. Oviposition

The time taken by the snails to start egg-laying varied from tray to tray and also from experiment to experiment as follows :

	having aestivated	not having aestivated (controls)
	days	days
Experiment I :	2—6	2—4
Experiment II :	4—14	2—14
Experiment III :	5—21	1—4

The total number of egg-masses laid by the snails in the first two experiments in 4 weeks were (versus without aestivating) : Experiment I : 233 vs. 133 ; Experiment II : 256 vs. 174. In both these experiments the differences were statistically significant ($p < 0.0005$).

Unfortunately the comparison in the third experiment lasted only 18 days because by then all the control snails had died. Up to that day the latter had laid 148 egg-masses (of which 74 were laid in the first week and 66 in the second week) against 47 egg-masses laid by the snails which had been aestivating. However, the latter went on to lay a total of 254 egg-masses, of which 112 and 126 were laid during the third and fourth weeks respectively. In the statistical analysis the mortality rates (see below) were taken into account.

3. Mortality rates

In experiment I there was a slightly higher mortality rate among the snails that had aestivated than in those that had not, so that at the end of 4 weeks there were 62 survivors in the former group as compared to 78 in the latter. In the second experiment mortality rates were more or less equal and both higher than in the first, with 17 and 23 survivors respectively. In the third experiment there were 44 survivors in the control group up to day 14, but all then died rapidly within the following 4 days ; there were 45 survivors in the group that had aestivated at the end of 4 weeks.

4. Size of egg-masses and number of embryos per egg-mass

The sizes of the egg-masses and number of embryos per egg-mass were recorded only in the second and third experi-

ments. No appreciable differences were found in both size of mass and number of embryos per mass, in 50 measurements for each group. The figures are summarized in Table 2.

TABLE 2. Oviposition rates, average size of eggmass and number of embryos per egg-mass in 3 *Bulinus* (P.) *nasutus* populations after aestivation and their controls.

	Population I		Population II		Population III*	
	Aest.	Control	Aest.	Control	Aest.	Control
Number of snails at start	80	80	80	80	60	60
Total number of eggmasses laid in 4 weeks . . .	233	133	256	174	254	148
Average size of 50 eggmasses (mm)	—	—	5.5	6	6	6
Average number of embryos in 50 eggmasses . .	—	—	11	13	17	18
Number of survivors after 4 weeks	62	78	17	23	45	—

(*) See text.

Discussion

Webbe (1962) in a 2 year study of the transmission of *Schistosoma haematobium* near Mwanza, Tanzania, observed a rapid build up of *B. (P.) nasutus* population after periods of desiccation. He concluded, as did Shiff (1964), that rainfall may, under certain conditions, stimulate bursts of breeding activities. So far there has been no evidence in support of increased oviposition rates soon after aestivation (McCullough et al., 1968).

In the present studies, although the control snails which had not aestivated laid slightly more egg-masses during the first week than those having aestivated, there was no striking difference in oviposition rates between populations I and II during that period (Fig. 1) whereas, in population III, the difference was appreciable. The 2nd, 3rd and 4th weeks revealed a statistically significant difference ($p < 0.0005$) between popula-

tions I and II. In the 3rd population, although the comparison lasted only 18 days, the oviposition pattern by the snails that had aestivated was followed up the full 4 weeks and revealed a striking similarity to that in population I and II (Fig. 1), i.e., a rather slow beginning in the first few days, then a sudden rise during the 2nd and 3rd weeks. Four weeks were thought to be a long enough period for the snails to adapt themselves to the new conditions in the laboratory and, in the field, the period might be even shorter.

B. (P.) nasutus prefers temporary to permanent habitats. McCullough et al. (1968) were of the opinion that this species might be evolving towards an amphibious mode of life, with aestivation apparently playing a big role in the survival of the species. Thus the findings in the present studies add yet another point in favour of that opinion.

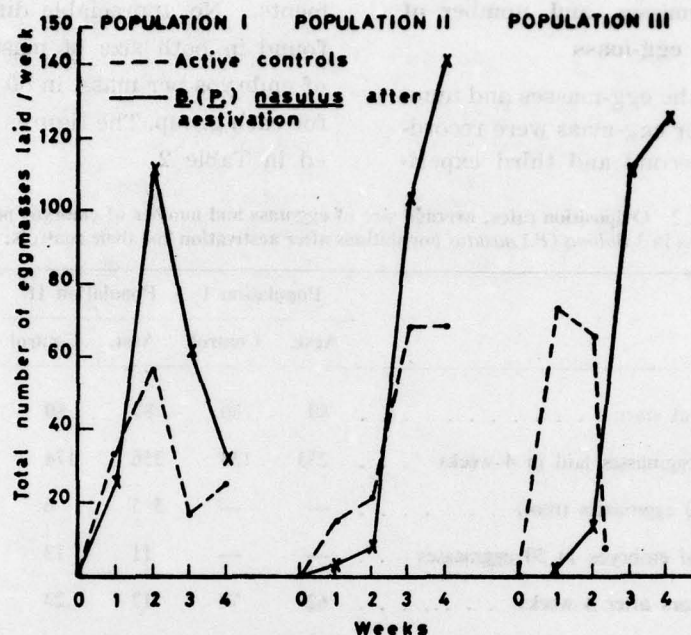


Fig. 1. Oviposition in 3 populations of *Bulinus (P.) nasutus* after aestivation and in their controls in the laboratory for 4 weeks.

In practical terms the significance of the present study lies in the application of snail control operations. Often the very temporary habitats, such as old rice paddies, furrows, etc., in the vicinity of the transmission site, serve more as reservoirs for *B. (P.) nasutus* than as active transmission sites for *Schistosoma haematobium*. Thus the search for habitats should be made at the very beginning of the rainy season in order to locate not only the obvious potential habitats but also the very shallow ones which dry out quickly. These, too, should be molluscicided.

Probably more important is the timing of molluscicidal operations. Webbe (1962) and McCullough et al. (1968) observed the highest snail counts at the beginning of the dry season. As a result, the local practice has been, hitherto, to molluscicide towards the end of the wet season so as to kill the maximum number

of snails and also to conserve the molluscicide which would otherwise be washed away by the flowing water. These two authors, however, noted also that the aestivation process probably begins before the severe contraction of the water bodies. Should, therefore, the results of the present studies be confirmed by further experiments, it might be worthwhile to try and kill the snails at the beginning of the rainy season soon after the aestivation period so that the animals are denied the opportunity of multiplying and/or aestivating in preparation for the next period of unfavourable conditions. Depending on the availability of funds, mollusciciding both at the beginning and end of the rainy season, as suggested by Webbe (1962), would be even more effective. An ovicidal molluscicide would be the chemical of choice. Pesigan et al. (1958), working in the Philippines, noted

that «prevention of breeding is more important than success in killing the snails that are present».

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EFFECT OF TWO MOLLUSCICIDES ON THE LEECH *HELOBDELLA PUNCTATO-LINEATA*, A NATURAL ENEMY OF THE VECTOR SNAILS OF BILHARZIASIS

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ABSTRACT

Several aquaria in our laboratory utilised for breeding and maintaining *Biomphalaria alexandrina* and *Bulinus truncatus*, the snail hosts of schistosomiasis in Egypt, became infected with leeches. These leeches were feeding on snails of all sizes, though they showed a preference for small snails. The leech, whose natural distribution coincides with that of the vector snails, was identified as *Helobdella punctato-lineata* (Hirudinea: Glossophoniidae).

As the predatory feeding habits of the Glossophoniidae with respect to aquatic molluscs have previously been referred to in the literature, a series of experiments were carried out to determine the extent to which the species identified was capable of adversely affecting *Biomphalaria alexandrina* populations. It was shown that these leeches are not predacious on *Biomphalaria* egg masses but that they readily attacked young snails, particularly the newly hatched snails which

were rapidly devoured, while losses among adult snails were no greater than among their controls. At the end of an observation period of 60 days it was shown that the initial snail population, of adult and juvenile snails in the aquarium harbouring leeches and in the control aquarium was reduced by 84% and 14% respectively; hundreds of juvenile snails were found in the latter and none in the former aquarium.

The effect of the molluscicides currently used in our country on the leech population was investigated in another series of experiments. It was shown that in molluscicidal concentrations copper sulfate did not affect the leeches, while a 100% mortality was attained within a few minutes after the application of Bayluscide.

The possibilities of the use of leeches alone or in combination with weak concentrations of copper sulfate applied for prolonged periods are discussed.

A MIRACIDIUM TRAP FOR USE IN FLOWING WATER

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ABSTRACT

Caged laboratory-reared snails can be used to detect miracidia in field sites. The method is useful for monitoring miracidial densities in situations where snail populations are unstable or where molluscicides are in use.

The technique has been used routinely on the island of St. Lucia, West Indies, to monitor the effect of various methods of schistosomiasis

control. Except in areas of massive contamination, infection rates are very low and only by the use of impractically large numbers of snails could minor changes in miracidial density be detected.

Substantial improvement in sensitivity may result from the use of cages designed to increase the opportunities for miracidium/snail contact.

ASSESSMENT OF LARGE SCALE MOLLUSCICIDING IN THE HAFT TAPPEH SUGAR CANE PROJECT, KHUZESTAN, SOUTH WEST IRAN

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ABSTRACT

The Haft Tappeh area is one of the foci of schistosomiasis in the endemic area in Khuzestan Province. The area contains 10,651 hectares of irrigated sugar cane plantation. Surrounding villages have a population of 11,181 individuals and an overall infection rate of 8.46% of urinary schistosomiasis. The irrigation system consists of 175 km of canals, 130 km of drains and 14 night storage reservoirs. Head water is obtained from

a lined canal (30 m³/sec.) which is supplied by water from the Dez River. The system was treated with Bayluscide in June 1974. It was found that for interruption of transmission, one general application must be applied in late spring and focal treatment over the rest of the year. The cost of one general application of molluscicide was found to be about US \$12,507.